Exhibit 7

Expert Witness Report and Declaration of Suzanne Parisian, MD

I. Qualifications

1. Since August 1995, I have been President and founder of Medical Device Assistance, Inc., a regulatory and medical consulting firm specializing in matters involving the United States Food and Drug Administration's regulation of products. I received my Medical Degree (M.D.) from the University of South Florida in 1978 and have been Board Certified in Anatomic and Clinical Pathology since 1989. I have also been a general practitioner and President of Mountain Emergency Physicians. I have a Masters in Biology from the University of Central Florida (minor in developmental biology).

2. From 1991 to 1995, I served as a Commissioned Officer in the United States Public Health Service and achieved the rank of Commander. During the time period, I was primarily assigned to the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA). Concurrently, I was also assigned clinical responsibilities at the Armed Forces Institute of Pathology (AFIP), Office of the Medical Examiner for the Armed Forces, Washington, D.C.

3. From 1991 to 1993, I was an FDA Medical Officer in the Office of Health Affairs (OHA), a staff office within the Center for Devices and Radiological Health (CDRH), FDA. In OHA, I provided regulatory support to both FDA's Office of Compliance and Office of Device Evaluation. My responsibilities in OHA included health hazard and health risk assessment, Safety Alerts and physician and layperson communications, review of adverse event reports and medical literature and review of product labeling,

promotions, advertising, and corporate records as to compliance with the Food, Drug and Cosmetic Act. I was responsible for the review of mandatory adverse event reports submitted by manufacturers, as well as the review of voluntary reports submitted by health care providers, patients and others. I presided over 162 health risk assessments convened to advise FDA on overall health risk issues for the public and made recommendations to FDA regarding the subsequent regulatory actions, which should be undertaken by FDA, health care providers, users groups and manufacturers to help protect the public's welfare. My assignment at OHA specifically included safety issues involving cardiovascular products. I participated in mandatory recalls and participated in hearings as FDA's expert witness.

4. From March 1993 to December 1993, I was a Medical Office in the Office of Device Evaluation (ODE), Division of Reproductive Abdominal, Ear, Nose and Throat, and Radiology (DRAERD), FDA, January 1994 through June 1995; I was one of two Chief Medical Officers in ODE. ODE, in contrast to OHA, is primarily responsible for premarketing evaluation of new product applications and clinical trials to support safety and effectiveness to begin legal marketing within the United States. In ODE, I participated in the review of proposed clinical trial, pre-marketing applications, including review of animal toxicology and biocompatibility data, as well as had the assigned responsibility of training new medical officers and scientific reviewers in application, clinical trial and labeling evaluation. I was the primary reviewing medical officer in charge of premarketing approval applications required to adhere to CDER's Drug Guidances, for presentation at the FDA Advisory Panel with members from CDRH and Center for Drug Evaluation and Research (CDER). Examples of other safety issues

involved FDA's evaluation and safety alert and market withdrawal for cauda equina syndrome associated with continuous spinal anesthesia and safety alert for precipitation of anaphylactoid reactions by ACE inhibitors. I was a primary author for FDA's guidance for Hemodilayzer Reuse labeling. I consulted as a medical officer on INDs for combination products including drugs and biologics. While in ODE, I conducted an additional 100 health risk assessments and was required to train medical officers as to methods for heath risk assessments, health hazard evaluations, annual report, adverse event and labeling review.

5. I was an initial instructor in FDA's Staff College for FDA reviewers training in the design and evaluation of clinical data in investigational and premarketing applications. I had primary responsibility for review of marketing applications, labeling and was required to teach medical officers the process for evaluation and review as required by the Food, Drug and Cosmetic Act for support of product marketing. I was charged with training medical officers on the process for health risk assessment and health evaluation per 21 CFR Part 7.

6. Regarding post market surveillance of marketed products, I participated with FDA's District Offices, Office of General Counsel, and the Office of Compliance in the review of manufacturing records, labeling, product complaints and adverse event reports obtained by FDA. I was the primary clinician involved in several of FDA's Major Corporate-Wide Actions for which I received various citations and honors for my services to the FDA, including Department of Health and Human Services and the Federal Government Employee of the Month.

7. I was sent by the FDA to serve as an official Agency representative to medical meetings and seminars to help identify and monitor conduct of manufacturers for potential deviations from regulations governing promotional activities. At those interactions, I was required to provide official guidance as to the FDA's interpretation of Food and Drug Laws as they pertain to medical products and the roles of manufacturers and health care providers.

8. While at FDA, I helped draft agency documents, guidance regarding requirements for obtaining FDA's marketing approval, FDA Safety Alerts, provided FDA comments for voluntary warnings and physician and user notifications, agency comments on voluntary industry standards. I was a FDA liaison with the National Institutes of Health (NIH) for issues involving ENT, Renal, Respiratory, Women's Health, and Alternative Medicine. I was required to provide support to Health Care Financing Agency (HCFA now CMS) regarding FDA's approval of product and issues involving hemodialysis. I was assigned responsibility for product adverse event reporting to the Department of Defense (DOD) and Veterans Administration.

9. One of my assigned responsibilities at FDA, using my training and experience, was to review facts contained in product marketing applications, clinical trials, medical literature, reports of post marketing experience, and available manufacturing documents gathered by FDA or provided to FDA by the manufacturer or other regulatory agencies, and then to use those facts 1) to make a clinical determination to a reasonable degree of medical certainty for FDA per the FDCA and 2) recommend the next courses of action available to FDA to protect the public health. I was also required by FDA to advise and train other FDA employees regarding the review of facts of a case or issue, the

requirements of the Food, Drug and Cosmetic Act, and making a determination to a reasonable degree of medical certainty the clinical impact of the agency's actions to the public. This was a process I was trained in and required to perform for FDA, and the health risk assessment process is further described in 21 CFR §7. During my tenure at the FDA, I reviewed hundreds of marketing applications for safety and efficacy as well as proposed draft labeling. In this capacity, I worked with industry scientists and academic clinical investigators for evaluation, marketing and labeling review of new products. I organized national conferences with industry and physicians to discuss and obtain expert consensus regarding the development of new products and labeling as well as evaluating existing products on the market for safety and efficacy.

10. At the Armed Forces Institute of Pathology (AFIP), Office of the Medical Examiner, I was required, again based on my training and experience in pathology, to take all available facts surrounding a patient's death and any involved adverse events and make a final determination: 1) to a reasonable degree of medical certainty, as to the cause of death, and 2) to recommend the next steps that should be taken by the military or another agency of the federal government. In that capacity as a Medical Examiner, I provided support to the various legal staff of the armed services, as well as the FBI and CIA. While a medical examiner at the AFIP, I determined that a cause of civilian patient deaths, of occurring in military hospitals, to a reasonable degree of medical certainty appeared to have been associated with unanticipated drug/device effect. I then reported my findings as MedWatch report to the FDA. As an AFIP Medical Examiner, I was able to trigger the FDA to investigate a major drug regulatory safety action which resulted in the protection of public health.

11. After leaving FDA, and founding Medical Device Assistance, Inc., I have continued to provide information to individuals, manufactures, and organizations outside of FDA's requirements, Adverse Event Reporting, and labeling of FDA-regulated products. Those products have included INDs, NDAs, IDE, PMAs, and 510(k)s for devices, biologics and drugs. I was requested by FDA to participate in a 1997 panel of experts convened by FDA to comment on changes proposed in the requirements for medical device labeling. I continue to consult for manufacturers, lecture at conferences and seminars regarding FDA, premarket clearance, design of clinical trials, product labeling, Corrective and Preventive Action (CAPA) and Quality Systems. I am the author of FDA Inside and Out published in May 2001 which is a book regarding the history and processes and use of the Food and Drug and Cosmetic Act and regulations by all six centers of the FDA.

12. A copy of my most recent C.V. is attached in Exhibit 1. I receive $350/hr for study and $475/hr for deposition and trial testimony.

II. Background Information Regarding FDA

A. The FDA and Regulation of Industry in the United States

13. The United States Congress mandated that the Federal Food and Drug Administration (FDA) be the federal agency charged to oversee public health and welfare for medical and therapeutic products including drugs, biologics products, and medical devices per the legal authority given to it through the Federal Food and Drug Act (FDCA) and subsequent amendments.

14. Between 1938 and 1962, FDA approved new drug applications as "safe", based on general support of safety and with limited amount of documentation required for a

sponsor to support "safety". However, FDA received a new mandate from Congress on the wake of the thalidomide scare and subsequent public outcry by the passage of the Kefauver-Harris Drug Amendment of 1962. The amendment required that FDA ensure that all new drugs post 1962 were approved for United States marketing with scientific support for safety and efficacy. The amendment required that the sponsor provided scientific support of safety and efficacy in the form of a new drug application (NDA) (21 CFR part 314) published 1985.

15. Significantly, the Kefauver-Harris Amendment contained a "grandfather" clause for products already on the market prior to 1962 – the date the Amendment became law. The grandfather clause provided that drugs commercially marketed prior to October 9, 1962 and after June 25, 1938, which would include Provera, approved by the FDA in 1959, were deemed safe and were not to be considered new drugs under the new Amendment provided that the products had not significantly changed in labeling or formulation and could support efficacy. As a grandfathered drug, Provera was not required to satisfy the current regulatory safety and efficacy standards applicable to pharmaceuticals. Provera was required only to pass a DESI review for support of efficacy, as described below.

16. For grandfathered products, in lieu of the sponsor having to submit a completely New Drug Application (NDA) to FDA for support of "efficacy", FDA created an alternative review process that would allow the sponsor to support efficacy and remain on the market. The process was called the Drug Efficacy Study Implementation (DESI) process. To facilitate the retrospective review process, the FDA would utilize outside consultation with experts of the National Academy of Sciences- National Research

Council. A formal contract was made between the FDA and the National Academy of Science with the FDA funding the project. FDA projected that the entire DESI process would take 2 years to complete, which proved to be an overly optimistic estimate. Meanwhile, FDA requested "voluntary action" to be started by the drug manufacturers and distributors of pre-1962 grandfathered drugs with modification and/or removal of unsupported promotional claims for grandfathered drugs. The agency also initiated the administrative actions necessary to require that manufacturers make product and labeling changes based on FDA's review and findings regarding efficacy.

17. At the request of the FDA Commissioner, the National Academy of Sciences-National Research Council (NAS-NRC) conducted a review of the groups of drugs on the market prior to 1962 and submitted recommendations to assist FDA in making final judgments regarding the support for "efficacy" of individual drug formulations. The Academy, after organizing and appointing 30 panels of experts, examined the literature and supporting data provided by the sponsors as to efficacy for approximately 4000 grandfathered prescription drug formulations.

18. The FDA responded to the NAS-NRC's recommendations by establishing its own method for internal review of the received NAS-NRC results of the DESI Project. The reports created by the NAS-NRC and other available data for the prescription drugs were internally reviewed by FDA's scientists in the Office of Drug Research and Review and were reported to a DESI PMS Project Manager of the DESI Project. These results and recommendations of the FDA were periodically published in the Federal Register as "Implementation Notices".

19. The FDA was required to take action on the DESI drugs based on its findings of the DESI Review and to withdraw all grandfathered "safe" products from the market when "efficacy" for an indication could not be supported. The FDA was also, at some point, to notify generic drug manufacturers of the outcome for the brandname or pioneer drug. Since DESI would have already demonstrated efficacy for the grandfathered safe marketed pioneer drug, the generic drug manufacturers were not required to duplicate the process. The generic drug version could obtain approval from FDA based on the recommendations of the DESI Review Panel for the grandfathered pioneer drug.

20. Using the findings and process of the DESI Review Panel, FDA took into consideration the abbreviated new drug application (ANDA) for generic drug approval. The ANDA application would be based on a generic drug firm providing FDA with documentation of the "sameness" of the active ingredients and "bioequivalence" to the pioneer drug. The DESI Review recommendations were codified for ANDAs in the 1984 Amendments to the Act. All prescription drug labeling was to be revised by a sponsor within 90 days of the publication in the Federal Register of the conclusions of the FDA or by May 15, 1972 unless the product was specifically exempted (21 CFR 201.200). In 40 FR 13998, March 27, 1975, the following was published regarding the requirements to disclose the efficacy findings of the DESI review process:

> **Sec. 201.200 Disclosure of drug efficacy study evaluations in labeling and advertising.**
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> (1)(1) The National Academy of Sciences-National Research Council, Drug Efficacy Study Group, has completed an exhaustive review of labeling claims made for drugs marketed under new-drug and antibiotic drug procedures between 1938 and 1962. The results are compiled in "**Drug Efficacy Study, A Report to the Commissioner of Food and Drugs from the National Academy of Sciences** (1969)." As the report notes, this review has made " an audit of the state of the art of drug usage

that has been uniquely extensive in scope and uniquely intensive in time" and is applicable to more than 80 percent of the currently marketed drugs. The report further notes that the quality of the labeling claims, is poor. Labeling and other promotional claims have been evaluated as "effective," "ineffective," "probably effective," "possibly effective," "ineffective," "ineffective as a fixed combination," and "effective but," and a report for each drug in the study has been submitted to the Commissioner.

(2) The Food and Drug Administration is processing the reports, seeking voluntary Action on the part of the drug manufacturers and distributors in the elimination or modification of unsupported promotional claims, and is initiating administrative actions as necessary to require product and labeling changes.

(3) Delays have been encountered in bringing to the attention of the prescribers of prescription items the conclusions of the expert panels that reviewed the promotional claims.

(b) The Commissioner of the Food and Drugs concluded that:

> (1) The failure to disclose in the labeling of a drug and in other promotional material the conclusions of the Academy experts that a claim is "ineffective," "possibly effective," "probably effective," or "ineffective as a fixed combination," while labeling and promotional material bearing any such claim are being used, is a failure to disclose facts that are material in light of the representations made and causes the drug to be misbranded.
>
> (2) The Academy classification of a drug as other than "effective" for a claim for which such drug is recommended establishes that there is a material weight of opinion among qualified experts contrary to the representation made or suggested in the labeling, and failure to reveal this fact causes such labeling to be misleading.

(c) Therefore, after publication in the Federal Register of a Drug Efficacy Study Implementation notice on a prescription drug, unless exempted or otherwise provided for in the notice, all package labeling (other than the immediate container or carton label, unless such labeling contains information required by 201.100(c)(1) in lieu of a package insert), promotional labeling, and advertisements shall include, as part of the information for practitioners under which a drug can be safely and effectively used, an appropriate qualification of all claims evaluated as other than "effective" by a panel of the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, if such

> claims continue to be included in the indications section of the portion of the advertisement containing the information required in brief summary by 202.1(e)(1) of this chapter. When, however, the Food and Drug Administration classification of such claim is "effective" (for example, on the basis of revision of the language of the claim or submission or existence of adequate data), such qualification is not necessary. When the Food and Drug Administration classification of the claim, as stated in the implementation notice, differs from that of the Academy but is other than "effective," the qualifying statement shall refer to this classification in lieu of the Academy's classification.
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> (e)(1) In drug labeling the box statement may entirely replace the indications section…..
> Final classification of the less-than-effective indications requires further investigation..
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> (f)(2) Less-than effective indication(s) in the promotional message of an advertisement which is a single package or less shall be keyed to the boxed statement by asterisk, by an appropriate statement, or by other suitable means providing adequate emphasis on the boxed statement. On each page where less-than-effective indications(s) appear the …. The asterisk shall refer to a notation on the bottom of the page which shall state," This drug has been evaluated as probably effective (or possibly effective whichever is appropriate) for this indication" and "See Brief Summary" or "See Prescribing Information," the latter legend to be used only if the advertisement carries the required information for professional use as set forth in 201.100 (c)(1).
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> (g) The Commissioner may find circumstances are such that , while the elimination of claims evaluated as other than effective will generally eliminate the need for disclosure about such claims, there will be instances in which the change in the prescribing or promotional profile of the drug is so substantial as to require a disclosure of the reason for the change so that the purchaser or prescriber is not misled by being left unaware through the sponsor's silence that a basic change has taken place. The Food and Drug Administration will identify these situations in direct correspondence with the drug promoters, after which the failure to make the disclosure will be regarded as misleading and appropriate action will be taken.

21. In a decision handed down in July 29, 1975, the U.S. District Court had held that a drug declared to be a "new drug" could not be marketed in the U.S. unless it was

covered by an "approved" new drug application per 21 U.S.C. § 321(p)(1970).[1] Presence of a filed NDA submission with FDA was not adequate. The same held true for identical or similar drug products. Thus sponsors were required to obtain an "approval of a completed drug application" from FDA as the only acceptable basis to allow the start of US marketing. In the Federal Register dated September 23, 1976, Congress announced the availability of a guideline for already marketed drugs which had not received approved NDA or ANDA and the steps that would be required to continue US marketing.

22. The DESI review process required industry and the FDA to review the medical literature to support "efficacy". The "paper NDA" was an attempt to continue a similar process using the available medical literature rather than conducting drug pre-clinical and clinical testing to support the safety an efficacy of marketing similar or identical drugs. The FDA's paper NDA review process did not appear to require as much time and work for FDA or industry to obtain approval to marketing similar products. FDA and industry sought a quicker method, expanding upon the NDA and DESI Review policies to provide for development and marketing of generic drugs for certain post-1962 drugs. The result was FDA's short-lived "paper NDA" policy, which was an attempt to bridge between the "old drug" and the "generally recognized as safe and effective" (GRASE) approaches for approval of drug marketing.

23. The paper NDA permitted competing versions of already approved post-1962 drugs to be approved by FDA based on submission of publicly available reports of well-controlled studies which could support a drug's safety and efficacy. However, adequate well-controlled studies were not generally available in the literature which could meet the

[1] Hoffmann-LaRoche, Inc. v Caspar W. Weinberger, Sec. of Health, Education & Welfare, et al. U.S. District Court for District of Columbia, July 29, 1975.

Act's requirements for valid scientific evidence. The paper NDA could prove to be as slow and tedious a process as obtaining approval of a traditional NDA.

24. FDA's "paper NDA" policy was challenged by industry. The court upheld the challenge.[2]

B. The Investigational New Drug Application (IND) (21 CFR Part 312)

25. The Investigational New Drug (IND) regulations were published in 1987, 52 FR 8831, after the commercial marketing of Provera by Upjohn. 21 CFR 312 defined for industry the procedures and requirements for a pharmaceutical firm to use in order to submit an investigational protocol to request to begin to study an investigational new drug in humans. The IND regulations were released after the NDA regulations. The FDA first approves the start of an IND exemption before a sponsor can begin using a new drug for treatment of humans. The IND process allows transportation in interstate commerce of a new drug/or drug for new indications which has not yet been demonstrated as safe and effective and allows the product not to be considered adulterated or misbranded under the requirements of the Act. The IND is a mechanism allowed by the Act to allow the ethical start of early clinical investigation of safety and later efficacy of potential new drugs in humans. The IND protocol helps assure the quality of the data which will be generated by the study and helps ensure safety and ethical treatment of subjects volunteering to participate in a clinical drug investigation.

26. As described in 21 CFR 312.22 published in 1987, **Phase 1** trials are closely monitored studies which have been designed to determine the metabolism and

[2] Hoffmann-LaRoche, Inc. v Caspar W. Weinberger, Sec. of Health, Education & Welfare, et al. U.S. District Court for District of Columbia, July 29, 1975.

pharmacologic actions of the drug when used in humans, they often use normal volunteers, the possible side effects which may be associated with increasing doses, and if possible to obtain early evidence of effectiveness. Phase 1 trials range from 20 to 80 subjects depending on the drug. During **phase 2 studies**, the sponsor begins to conduct "controlled clinical studies" designed specifically to help evaluate safety but now include effectiveness of the drug for a particular indication in patients with a disease or condition under study using specified endpoints. Phase 2 trials are usually on a small group of patients, usually no more than several hundred. **Phase 3 studies** are "expanded controlled and uncontrolled" clinical trials which are performed as primary support for effectiveness of the drug and which will be included in marketing applications to support product approval. Phase 3 studies are intended to gather additional information needed to help evaluate the overall benefit-risk relationship of the drug and provide a basis for proposed physician labeling. Phase 3 trials can range from several hundred subjects to several thousand. Phase 4 studies (21 CFR 312.85) are studies which are required to be conducted by FDA after NDA approval. Concurrent with new drug marketing approval, FDA may seek an agreement from the sponsor to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

27. For post 1962 "new" drugs, the Act and IND regulations require FDA to monitor ongoing clinical studies being conducted by sponsors and submitted in marketing

applications. However, FDA has limited resources. It would be virtually impossible for the FDA to reach out to all clinical investigational sites or facilities and monitor ongoing clinical investigations. The responsibility for monitoring the conduct of clinical investigators at each investigational site and the safety of the subjects enrolled and fulfillment of endpoints in clinical trials rests under the Act with the clinical trial sponsor and its selected monitors, such as Drug Safety Monitoring Board (DSMB), Contract Research Organizations (CRO) . For each IND clinical trial there is to be documentation of obtaining signed voluntary informed consent (21 CFR part 50) and oversight by an Institutional Review Board. (IRB) (21 CFR part 56). The monitoring of clinical investigation quality and patient safety is critical to the general mission of the FDA to ensure the quality of the scientific evaluation of drugs as to safety and effectiveness (21 CFR 312.22(a)). The FDA's ability to evaluate the data from clinical studies described in the marketing submission information is directly dependent on a firm's truthful, timely and balanced compliance with the regulations and Act and its candid disclosure to FDA of all relevant safety and performance information. 21 CFR 312.33 requires a new drug sponsor to file annual reports within 60 days of the IND anniversary date. The annual report is to provide FDA with a summary of the previous year's progress. The report is to include a summary of both clinical and nonclinical data for the IND and new drug. 21 CFR 312.32 also requires the sponsor to file IND Safety Reports with FDA and review of safety information:

> (b) *Review of safety information.* The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports

from foreign regulatory authorities that have not already been previously reported to the agency by the sponsor.

28. As a medical review officer for the FDA, faced with the review of many new product applications, it was necessary to assume until proven otherwise that each sponsor would behave ethically and provide the agency with truthful and accurate information. The medical review of clinical data for support of valid scientific evidence of safety and efficacy in marketing applications is identical for drugs, devices and biologics.

C. The New Drug Application (NDA) (21 CFR Part 314)

29. After completing its IND, designed to specifically support safety and effectiveness of a new drug for a new indication (or indications) and/or specific new intended patient population, a sponsor submits an NDA to the FDA to request approval for commercial marketing. The IND information is summarized in the NDA. It is the responsibility of the sponsor of an NDA to provide FDA with all relevant safety information and to highlight for FDA any safety concerns remaining for the drug.

30. Upon receipt of the NDA, the FDA distributes and assigns the NDA to appropriate Division Director or Drug Evaluation Office Director in CDER who in turn assign the NDA application to reviewers under a designated team leader. The team leader can refer specific sections to other specialized reviewers of CDER or utilize review skills from other Centers of FDA. The NDA review includes the information provided by the sponsor. The reviewer documents his findings by generating and official written report with recommendations to be included in the official FDA review record. The supervisors from the Director of the Division up to the Commissioner of the FDA

have the authority to accept or reject each reviewer's findings and recommendations regarding the NDA. At the conclusion of the new drug review process, the NDA application will be approved, not approved, or the sponsor will be sent an "approvable" letter. If the NDA is not approved, the sponsor receives a not-approvable letter which identifies the remaining deficiencies which if addressed may be able to make the application "approvable". The sponsor can under some circumstances correct the deficiencies and resubmit additional information to the NDA to address FDA's remaining deficiencies and request reconsideration for approval. The "approvable" letter specifies the remaining conditions which must be met by the sponsor to make the product approvable.

31. The FDA utilizes Panels of Advisory Committees of outside independent experts to assess information provided to FDA by the manufacturer in the NDA application and provide recommendations to the FDA. The Advisory Panel may also be used by FDA to make public suggestions to FDA regarding the types of guidance which should be given to industry for marketing applications and/or safety issues. The Advisory Panel members present nonbinding recommendations to the FDA. The Advisory Panel can also make recommendations for product labeling issues and possible post marketing concerns which can be addressed by post approval studies.

32. The FDA approves or disapproves a new drug application for marketing based on its evaluation of risk versus benefit from the data obtained by the clinical trials in the NDA. Both industry and the FDA recognize the pre-marketing clinical trials will not be able to identify and predict all the potential risks that may occur following commercial

use, thus highlighting the need for appropriate phase IV clinical trials and postmarketing surveillance.

33. It is the sponsor's obligation – not the FDA's – to complete postmarketing requirements such as phase IV studies, provide FDA and physicians with adequate and truthful postmarketing reports (21 CFR 314.81), monitor performance and update product inserts and promotions.

Labeling Issues

34. Once an NDA is approved, the FDA and the sponsor begin negotiating the language of the draft product labeling and product insert. The sponsor begins the process with creation of its proposed draft labeling. The proposed labeling should reflect the data of the clinical trials as well as reported human performance. The sponsor, not the FDA, is responsible for compliance with adequacy of label requirements under the Act and for the adequacy of the contents of labels, labeling and promotions. Under 21 CFR 314.170, all new drugs, including those the FDA has approved under section 505 of the Act are subject to adulteration and misbranding provisions in sections 501, 502, and 503. The FDA regulates approved new drugs by regulations through informal rulemaking under sections 501, 502, and 503 of the Act.

35. Since the promulgation of the requirements set forth in Federal Register (41 FR 6908) on **February 13, 1976**, misleading statements in drug labeling have been described as:

> Sec. 201.6 Drugs; misleading statements.
> a) Among representations in the labeling of a drug which render such drug misbranded is a false or misleading representation with respect to another drug or a device or a food or cosmetic.

36. Under the definitions of the Act labeling and label are defined as follows:

> SEC. 201. [21 U.S.C. 321] For the purposes of this Act--
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> (k) The term "**label**" means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.
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> m) The term "**labeling**" means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.
>
> (n) If an article is alleged to be **misbranded** because the **labeling** or **advertising** is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

37. Since 1979 (44 FR 37462), the FDA's general format for prescription drug labeling are found in 21 CFR 201. 55. According to 21 CFR 201.57(e), the FDA drug regulations regarding labeling states that the "**warning**" section of a drug label shall describe serious adverse events and potential safety hazards and actions, limitations imposed by them and steps that should be taken when they occur. This section requires that "the labeling shall be revised to include a warning **as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.**" Further, in promulgating this regulation, the FDA stated:

> [L]abeling regulations do not prohibit a manufacturer...from warning health care professionals whenever possibly harmful adverse effects associated with the drug are discovered. The addition to labeling and advertising of additional warnings... is not prohibited by these regulations. 44 Fed. Reg. 37434.

A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard.

38. The FDA may require that special problems with a drug, particularly those that may lead to death or serious injury, to be prominently displayed in a **box at the outset of a package insert**. This "black box" warning contains information that is ordinarily based on clinical data, but serious animal toxicity risks may also be the basis of a boxed warning in the absence of clinical data. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "**Adverse Reactions**" section of the labeling.

39. In contrast to "Warnings," (21 CFR 201.57(f), the "**Precaution**" section in a drug label is to contain the following subsections as appropriate for a drug:

> (1) *General.* This subsection of the labeling shall contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug, e.g., precautions not required under any other specific section or subsection of the labeling.
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> (2) *Information for patients.* This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug,

> e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the "Precautions" section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling. The print size requirements for the Medication Guide set forth in 208.20 of this chapter, however, do not apply to the Medication Guide that is reprinted in the professional labeling.
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> (3) *Laboratory tests.* This subsection of the labeling shall identify any laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information shall be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be done before, during, and after therapy.

40. In light of safety or efficacy issues relating to a drug, or if a sponsor desires to improve the overall safety and effectiveness of a drug label to protect public health or comply with the Act, the drug's sponsor may add to or strengthen its warnings or otherwise change its label without the FDA's prior approval through a process discussed in **(21 CFR 314.70(c)(6)(iii)(A-D):**

> (6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:
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> iii) Changes in the labeling to accomplish any of the following:
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> (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;
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> (B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;
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> (C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

> (D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; ....

This section permits important labeling changes affecting public health and safety to be swiftly implemented by a manufacturer avoiding the delay a requirement for FDA's prior approval of a supplement would involve.

41. The role of the FDA is to enforce regulations that govern the pharmaceutical companies. The resources provided to the FDA, to accomplish this task, are limited. Drug companies know this. Drug companies cannot rely upon, and certainly cannot minimize their own responsibility and capacity to ensure the safety of the public from the dangers of the drugs it makes and profits from. Sponsors of FDA-regulated products are required to ensure product safety and provide adequate and truthful labeling. It would be illogical that the Act and FDA's regulations would not allow for a process whereby the NDA sponsor can immediately improve product labeling, protect public health and ensure its full compliance with the Act.

42. Since the Federal Register of February 13, 1976, misleading statements in labeling have been described as:

> Sec. 201.6 Drugs; misleading statements.
> a) Among representations in the labeling of a drug which render such drug misbranded is a false or misleading representation with respect to another drug or a device or a food or cosmetic.

43. Information placed in the "Contraindication Section" of a label describes those situations in which the drug should not be used because the risk clearly outweighs any possible benefit. Known hazards and not theoretical possibilities are to be listed, e.g., if

hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state, "None known." (21 CFR 201.57(d).)

44. The regulations require that the frequency of serious adverse events and other pertinent information "shall" be provided under the "adverse reaction" section of the label (21 CFR 201.57(g)). This section of the label "shall list the adverse reactions that occur with the drugs in the same pharmacologically active and chemically related class."

45. A drug's sponsor, not the FDA, is responsible for the content of both product labeling and a product's label. The sponsor, not the FDA, prepares the draft original label after NDA or sNDA approval, and it is the sponsor that is required to draft all additional or supplemental labels including any revised warnings sections. The regulations expressly state that labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not be proved (21 CFR 201.57(e)). "**Reasonable association**" can be provided by evidence of a variety of sources including:

a) in vivo and in vitro evidence collected during the preclinical period;
b) well documented single case report;
c) a case series;
d) adverse event analysis;
e) epidemiological studies (including observational studies); and
f) clinical trials.

V. History of Provera (NDA 11-839) (Medroxyprogesterone acetate or MPA)

46. George Spero of Kalamazoo, MI assigned US Patent 3,147,290 6α-17α,21-dihydroxy-4-pregnen-3,20-dione and 21-acetate patented September 1, 1964 to Upjohn

Company. The original Upjohn patent application for this group of related steroid compounds was a continuation of an application filed in November 23, 1956 and a division of an application filed February 19, 1958. The new products had utility as oral and parenteral progestational agents. The US Patent application stated that:

> Owing to their progesterone-like effects, the compounds of this invention find application in "cyclic" therapy, where estrogenic and progestational hormones are supplied together or in succession so as to favor re-establishment of normal endometrium-ovary-anterior pituitary relationships in cases of menstrual disturbances.

47. The United States trademark for the name Provera, identifying a progestational agent, was first used in United States commerce April 2, 1958 by Upjohn Company. The US Trademark Depo-Provera was first used commercially by Upjohn August 23, 1960. The original NDA 11-839 for Upjohn to market oral MPA was approved by FDA based on support for safety on July 3, 1959.

48. The Brook Lodge Symposium: **Progesterone**, was published by Brook Lodge Press, Guest Editor Allan C. Barnes, MD, copyright 1961, The Upjohn Company, Kalamazoo, MI. (NDA-PRO 0055839). Upjohn submitted this paper in support of the MPA efficacy review which was conducted by the NAS-NRC DESI group and FDA. The symposium text contains 9 sections dealing with the role of progesterone/progestins during pregnancy or to identify pregnancy. It also had the following other sections: Hyperplasia and Carcinoma In Situ of the Endometrium authored by R. Kistner; The Effect of 6α-methyl-17α-acetoxyprogesterone on the Endometrium, authored by HW Boschann and R Drews; The parenteral effectiveness of 6-methyl-17α-OH- progesterone acetate Under Varying Dosages of Estrogenic Priming of the Endometrium in Surgical

Castrates, authored by Dr. Wied and Davis; and 6-methyl 17-acetoxy-progesterone Injectable: Clinical Experience, authored by W. Barfield and R. Greenblatt.

49. The "Effects on Endometrium" study by Drs. Boschann and Drews of West Berlin, Germany utilized a "Kaufmann-scheme" for transformation of the endometrium. The Kaufmann-scheme has endometrium proliferation produced in surgically castrated females by 5 intramuscular injections of 5mg estradiol benzoate. Each patient is given 2 injections per week between the first and 15th day of her test cycle. Endometrial proliferation can be maintained by 2 injections of 5 mg estradiol given the 18th day and 22nd days. Oral 6α - methyl-17α-acetoxyprogesterone (Provera) was administered in 10 daily doses from the 15th to the 24th day. Parenteral injections of 6α - methyl-17α-acetoxyprogesterone (Depo-Provera) was administered on the 15th day and, two series, also on the 22 day of the test cycle. Endometrial biopsy was performed on the 28th day.

50. The study was part of a series of studies done by the authors for evaluation of 411 artificial cycles induced in 16 surgical castrate women, age range 32- 48 years. In order to obtain a satisfactory transformation of the estrogen-primed endometrium of surgical castrates the necessary oral doses of progestins studies had to be varied based on the different potencies.. In terms of potency, 6α -methyl-17α-acetoxyprogesterone proved to be 4 times as potent as 17α-ethinyl-19-nortestosterone…., 24 times as potent as 17α-ethinyl-testosterone, 28 times as potent as 17α-acetoxyprogesterone and **80-120** times as potent as chemically pure, orally administered progesterone. In order to obtain a satisfactory secretory transformation of the estrogen-primed endometrium in human surgical castrates parenteral (not oral) doses of progestins were necessary. Withdrawal bleeding occurred two days after the injection of 200mg chemically pure progesterone in

oily solution, eight days after the injection of 200 mg 17α-hydroxyprogesterone caproate (Hyalutin) and sixteen days after the injection of 50 mg 6α - methyl-17α-acetoxyprogesterone (Depo-Provera).

51. Drs. Wied and Davis continued with a similar study as Dr. Boschann had done in Germany. The authors concluded that "parenteral" (not oral) administration of progestational substances could induce in many cases of atrophic vaginal epithelium of castrates, women not previously treated with estrogens, some moderate proliferative changes of the squamous epithelium.

52. At the Medical College of Georgia, Drs. Barfield and Greenblatt re-examined the experience with injections (not oral) of 6α - methyl-17α-acetoxyprogesterone (Depo-Provera). The parenteral form of MPA was used since the oral effects (Provera) were reduced by liver metabolism and the effects could not be sustained as long in the body as the injectable formulation. The authors indicated that injection of Depo-Provera had a prolonged effect as a progestational agent and could raise the basal temperature in an anovulatory patient for as long as 4 to 6 weeks. With prolonged use it eventually caused atrophy of the endometrial glands and marked decidua-like changes in the stroma. Ultimately both the glands and the decidua-like effects were lost and a true atrophy occurred. The study suggested that Depo-Provera injections are clinically useful in the management of endometriosis and was satisfactory for the postponement of menstruation.

53. Dr. Kistner, Harvard Medical School and Free Hospital for Women, Brookline, MA discussed the association between endometrial hyperplasia and subsequent carcinoma in situ (CIS) with a relationship between the two noted to occur in females since 1904. He stated that:

> A fair summation of the data seems to be that "in predisposed individuals, the unopposed action of estrogenic substances for considerable periods of time will result in endometrial adenomatous hyperplasia, carcinoma in situ, and, eventually, carcinoma."
>
> Recent studies have suggested an endocrine correlation based on the findings of increased urinary excretion of adenohypophyseal hormone (LH) in patients with endometrial cancer. This may be related to the familiar background in these patients of prolonged anovulation, dysfunctional bleeding and infertility.
>
> A suggested method of prophylaxis against this progressive "unrest" of the endometrial epithelium has been to secure ovulation, menstruation and pregnancy. Unfortunately, most patients in this group never accomplish this goal.
>
> Another method of prophylaxis may be available in the use of certain newer progestins. Studies of LH excretion in patients with endometrial carcinoma have shown a diminution following administration of 17-alpha-hydroxyprogeterone caproate. Moreover, endometrial hyperplasia of varying degrees has been reversed by ovarian wedge resection....presumably by the subsequent cyclic action of endogenous progesterone.
>
> The conclusion may be drawn that, in anovulatory patients with endometrial hyperplasia, persistently elevated LH levels may be lowered by the action of endogenous or exogenous progesterone. Hyperplastic endometrial patterns are then reversible either because of the direct action of progesterone (or progesterone-like substances) on the glands or by their subsequent cyclic desquamation.

54. Patients in his subsequent case study had a retrospective review of uterine curettages as well as a prospective arm component. Four women were given 1) Enovid; or 2) Delalutin intramuscularly twice per week; or 3) Depo-Provera 100mg intramuscularly once per week prior to either surgery or curettage. The females all had varying etiologies of endometrial hyperplasia and carcinoma in situ. The only woman receiving Depo-Provera was postmenopausal, post mastectomy and had received a variety of continuous steroidal estrogen agents. The author wrote that:

> Although the specific morphologic changes preceding carcinoma of the endometrium are not adequately documented, some suggestive evidence has been advanced by Hertig and Sommers to indicate that adenomatous (atypical) hyperplasia precedes carcinoma. This study was based on a retrospective examination of prior curettings in women known to have endometrial cancer. However, several prospective experiments have been carried out which support the premise that **adenomatous hyperplasia does not always proceed relentlessly toward unequivocal carcinoma** and it is, at present, **impossible to predict which hyperplasia will, and which will not, develop a malignant potential.**
>
> Gusberg classified "atypical" hyperplasia as being histologically identical with adenomatous hyperplasia, carcinoma in situ and Stage 0 cancer. He followed 64 patients having this entity for five years and subsequently found invasive cancer in three (4.6%). Gusberg concluded that adenomatous hyperplasia may be present in the same endometrium with adenocarcinoma or it might be a cancer precursor....
>
> Wellenbach and Rakoff demonstrated in **oophorectomized hamsters** that induced endometrial hyperplasia underwent rapid regression when progesterone was given. They showed further that if progesterone was administered with estrogen, hyperplastic endometrial changes were virtually prevented. The newer progestins have been shown by us and others to produce specific and dramatic changes on the morphology of endometrial glands in adult, normally ovulating females. Following the initial secretory effect the gland lumina gradually become narrower and the epithelial cells assume a cuboidal appearance. If the progestin is continued, and ovulation prevented, the glands diminish in size, the lining cells become flattened and show no mitotic activity. Thus a state of glandular "regression" is produced. (emphasis added)

55. The author concluded that an approach using progestins with endometrial hyperplasia was not to be viewed as a cure or definitive therapy for patients in either the premenopausal or menopausal age groups. In young females every effort should still be made to secure ovulation so that a woman's own endogenous progesterone could be utilized.

56. The Brook Lodge Symposium contained no section specifically addressing the use of either Depo-Provera or Provera for treatment of menopausal symptoms. It

contained no section discussing the use of "combined estrogen-progesterone replacement therapy" for treatment of menopausal symptoms. There is no discussion of any well-controlled study providing scientific support for a reduction in cancer risk from estrogen due to the use of progesterone.

57. The following are the indications contained in Provera's 1965 labeling which were submitted for the DESI review of efficacy:

> **Indications and Dosage**
>
> **Replacement therapy** with progestational agents has been found useful in a number of conditions associated with pregnancy and menstruation including secondary amenorrhea, functional uterine bleeding, infertility, threatened and habitual abortion, dysmenorrhea and premenstrual tension. In the presence of a deficiency in endogenous progesterone, administration of Provera in adequate doses is capable of re-establishing normal cyclic menstruation, producing changes in the endometrium necessary for implantation of the fertilized ovum and maintaining pregnancy.
>
> **Secondary amenorrhea**
> The doses range from 2.5 to 10 mg daily depending upon the degree of endometrial stimulation desired and should be given daily for 5 to 10 days beginning on the assumed 16th to 21st day of the cycle.
> In patients with poorly developed endometrial, conventional estrogen therapy should be given in conjunction with Provera. Following this therapy, withdrawal bleeding usually occurs within three days. However, doses of 5 to 10mg daily for 10 days are required to produce a complete secretory endometrium. In order to promote the re-establishment of cyclic menstruation, treatment should be repeated for three consecutive cycles.
>
> **Functional Uterine Bleeding**
> In functional uterine bleeding progesterone therapy transforms the usual unshed hyperplastic proliferative endometrium into a secretory endometrium with subsequent control of the bleeding through rapid exfoliation of the endometrium following withdrawal of steroid therapy. In functional uterine bleeding, Provera may be given in doses ranging from 2.5 to 10mg for 5 to 10 days beginning on the assumed or calculated 16th or 21st data of the cycle.
>
> When bleeding is due to a deficiency of both ovarian hormones, as indicated in poorly developed proliferative endometrium, estrogens should

be used in conjunction with this product. If bleeding is controlled satisfactorily, two subsequent cycles of treatment should be given.

Infertility
Inadequate function of the corpus luteum may be a factor in infertility. Such dysfunction is reflected by a short secretory phase of the cycle, an inadequate temperature rise, low pregnanediol excretion during the luteal phase, and imperfect secretory endometrium at the end of the cycle. In this situation, Provera may be given at doses of 2.5 to 10mg daily during the first half of the cycle (14 days).

Habitual or threatened abortion
While the etiology of habitual or threatened abortion is incompletely understood, excretion studies have indicated that deficiency of endogenous progesterone may be an important factor. For this reason, progesterone replacement therapy is recommended in the management of these conditions. Recent clinical reports reflect a trend towards employing increasingly higher doses of progestational agents for this purpose. The recommended doses of Provera in these conditions are as follows....

Premenstrual Tension and Dysmenorrhea
Progestational agents are also being employed in patients with premenstrual tension and dysmenorrha. In these conditions the suggested doses of Provera are: premenstrual tension-2.5 to 10mg. for 5 to 7 days preceding expected menses; dysmenorrhea- 2.5 to 10 mg from the 5th to the 25th day of the cycle.

Pregnancy Test
Provera may be given to differentiate secondary amenorrhea from early pregnancy in patients in whom a normal pituitary ovarian functional relationship has been demonstrated. In the nonpregnant patient, medroxyprogesterone acetate will complete the endometrial cycle with resultant withdrawal bleeding. Since administration of this product does not disturb pregnancy, withdrawal bleeding will not occur. The recommended dose for this purpose is 10 mg daily for 5 days. If the patient is not pregnant, withdrawal bleeding will occur in from 2 to 7 days in the majority of patients.

58. On July 27, 1972,37 FR 15033, (DESI 11839), was published to announce the FDA's conclusion pursuant to the evaluation reports received from the NAS-NRC, DESI Group regarding Upjohn's Provera Tablets.

DESI Panel on Drugs Used in Disturbances of the Reproductive System

1. Secondary amenorrhea
EVALUTION: Effective
Comments: This preparation is useful for the induction of bleeding in patients with primary and secondary amenorrhea when the uterus is estrogen primed. The Panel emphasizes that this therapy does not induce ovulation.
DOCUMENTATION:
1. Brook Lodge Symposium: Progesterone. Brook Lodge Press, Augusta, MI, 1961, pp 1-220.

2. Functional uterine bleeding.
EVALUTION: Effective
COMMENTS: Numerous methods of designating the indication for abnormal uterine bleeding are employed, and generally the Panel believes then to be insufficiently precise. Until the terminology is standardized or clarified, a more appropriate statement would be that progesterone therapy is effective for abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer.
DOCUMENTATION:
1. Brook Lodge Symposium: Progesterone. Brook Lodge Press, Augusta, MI, 1961, pp 1-220.
2. Eichner, E. Clinical uses of a 17α-hydroxy-6a-methylprogesterone acetate in gynecologic and obstetric patients. Amer J. Obstet Gynec. 86: 171-176, 1963.
3. Greenblatt, R.B., and W.E. Barfield. The progestational Activity of 6-methyl-17-acetoxyprogesterone. Southern Med. J. 52:345-351.

III Infertility
EVALUATION: Possibly effective.
COMMENTS: An inadequate luteal phase can be a factor in infertility; however, the usefulness of this preparation has not been established by sound therapeutic trials and this indication should be considered inappropriate unless the manufacturer can supply adequate proof of efficacy in this situation.
DOCUMENTATION: None available.

IV. Habitual and threatened abortion
EVALUATION: Probably effective

V. Premenstrual tension and dysmenorrhea
EVALUTATION: possibly effective
Documentation: None available

VI. Pregnancy test
Evaluation: Effective

59. In a Follow-up by the FDA for DESI 11839, the agency wrote in October 1973 that based on new concerns about **prenatal safety** , use of progesterone/progestins in the prenatal period could not be recommended. The agency's actions significantly reduced the indications for use of all progestins. The change in the allowed indications curtailed a significant part of the promotion activities used for MPA for treatment of fertile women and during pregnancy. Previous Upjohn marketing MPA was as an effective ovulation inhibitory substance in the rabbit and could maintain pregnancy in ovariectomized rats with minimal androgenic effects. Upjohn had already become aware of received adverse event reports associating use of PMA during pregnancy with congenital malformations. FDA wrote that:

> In addition, data have become available which suggest a possible association of prenatal hormonal treatment of mothers with congenital heart defects in the offspring. The Food and Drug Administration has received available material and has presented the problem to its Obstetrics and Gynecology Advisory Committee. On the basis of these considerations it is concluded that a question of safety is raised by inferential evidence supporting the existence of an association between the administration of progestins during early pregnancy and the occurrence of congenital malformations. The potential risk of teratogenic effects is considered high enough to warrant removal of pregnancy-related indications from the labeling of progestins currently marketed for systemic use. Those indications, some of which were evaluated as effective, and others, as probably or possibly effective for the drugs listed above are:
>
> 1. Presumptive test for pregnancy;
> 2. Treatment of threatened and habitual abortion; and
> 3. Treatment of any abnormalities of pregnancy including pregnancy complicating diabetes.

60. On July 22, 1977 in the Federal Register FDA published **Progestational Drug Products for Human Use,** requirements for labeling directed to the patient for both estrogen and progestational drug products. The agency proposed to require that

manufacturers supply consumer labeling because of recent scientific reports that indicated that pregnant women who had used sex hormones during the first four months of pregnancy had increased risk for damage to the fetus. The new regulation specified the kind of information and warnings to be contained in the patient labeling and how it was to be made available to the patient. The regulation did not apply to progestagen-containing products intended for use for contraception. Due to the seriousness of the risk, the FDA's Commissioner opined that patient labeling was necessary to assure that the oral instructions of the physician were not misinterpreted or forgotten by the patient. The patient labeling was to reinforce what the physician had explained to the patient and was to serve as a written reminder to the patient during the course of her therapy.

B. NDA 11-839 Provera (Oral Tablets medroxyprogesterone acetate 2.5mg, 5.0mg, and 10mg)

61. Upjohn Company's oral medoxyprogesterone tablet was approved as NDA 11-839 for marketing based on the firm's claim of "safety" on July 3, 1959. As discussed above, at that time, there were no FDA requirements that a marketing application must be able to "scientifically" show support of safety and efficacy for an indication in an intended patient population.[3]

[3] The human drug IND regulations (21 CFR 312) for conducting ethical and valid human clinical trials were not published by FDA in 1987; the regulations (21 CFR 314) for the content, review, and process of a New Drug Application 1985; human drug labeling (21 CFR 201) regulations 1976; format for human prescription drug labeling (21 CFR 201.55) in 1979; establishment of Bioresearch Monitoring Program for oversight of clinical trials 1977; Institutional Review Board (21 CFR Part 56) 1981; Informed Consent (21 CFR 50) 1980; and Financial Disclosure by Clinical Investigators (21 CFR Part 54) 1998. The amendment to the Act which triggered DESI Review for support of "efficacy" was the 1962 Kefauver Harris Amendment, a response to a prenatal "safety" issue with Thalidomide. Investigational drug Thalidomide had not yet had an NDA approved as safe but it was already being widely distributed throughout the United States as an investigational drug without any FDA oversight or controls.

62. In 1959, the Upjohn Company had sent a Dear Doctor letter to physicians (NDA-PRO 0000929) touting the potency and safety of **95% Effective Provera for Treatment of Amenorrhea**.:

> This high rate of effectiveness at such a minute dose is directly attributable to the unparalleled potency of Provera. By comparison, Provera is thirty-six times more potent than ingested progesterone and twelve times as potent as ethisterone in inducing withdrawal bleeding in amenorrheic women.
>
> And coupled with this impressive potency is an unparalleled degree of safety for your patients.

63. Provera, prior to DESI, had a long history of being promoted to physicians for use combined with estrogen for hormone replacement therapy. An early example of such promotion is NDA-PRO 0029068. Though undated, this promotional material contains a reference dated 1966. This pre-DESI promotion clearly advocates the use of Provera to oppose estrogen's effects, and promotes the use of both hormones long-term. It reads, in relevant part:

> **The benefits**
> Cyclic therapy with Provera helps modify the effects (irregular bleeding) of continuous estrogen replacement.
>
> **Estrogen**- manage the symptoms- If you choose long-term estrogen treatment for your patients, then in addition to helping provide symptomatic relief....
>
> **PROVERA**- to manage the estrogen-
> ■ Periodic menses helps shed hyperplastic endometrium
>
> ■Estrogen/progesterone therapy may be maintained throughout the post-menopausal years to facilitate periodic shedding and generation of healthy, uterine tissue.

64. Similarly, a 1969 promotional piece (NDA-PRO 0029078-82) continues the theme of long-term estrogen use with the risks/effects counterbalanced by the addition of Provera:

> **Estrogen-** Aids symptomatic relief and long-term management of the menopause
> **Provera-** Helps control irregular menses. Modifies the effect of unopposed estrogen of the endometrium.

65. NDA-PRO 0000631 is another pre-DESI promotion made to physicians, this one entitled "The Glamorous Grandmother." This piece addresses unpredictable bleeding cause by administration of exogenous estrogen. Again, the message is clear – Provera is to be used as part of hormone therapy with estrogen in menopausal women. Further, the statement "Estrogen therapy for the menopause and beyond" suggests long-term use of exogenous estrogens, and consequently, the long-term use of Provera. According to this promotion, the benefits of adding Provera in combination with estrogen in hormone therapy in postmenopausal women are: 1) the reduction in irregular bleeding over time, and 2) the reduction of endometrial hyperplasia.

66. NDA-PRO 0028917 is yet another example of pre-DESI promotion of Provera for use in hormone therapy. This piece, copyright 1970, describes "The Upjohn Plan" which is the use of Feminone, an estrogen marketed by Upjohn, and Provera together in a combined hormone therapy.

67. The promotional items mentioned above are only a sample of the pre-DESI promotion of Provera to physicians for use with estrogen in hormone therapy. Additional

examples of similar promotional items are found in the Provera NDA files and the exhibits to David Engel's deposition.[4]

68. From the above examples of Provera marketing in the 1960s and early 1970s, it is clear that Upjohn actively marketed Provera to physicians for use in menopausal combined hormone therapy. As a result of the DESI review, Provera's efficacy for this use, or indication, proved to be unsupported.

69. As has already been discussed above, as a result of DESI, in 1972 Upjohn's Provera was deemed by FDA to be safe and "effective" for only the following limited indications: Secondary amenorrhea; and abnormal uterine bleeding (AUB) due to hormone imbalance in the absence of organic pathology such as fibroids or uterine cancer. Provera was not found to be effective for dysfunctional bleeding produced in menopausal females as a result of exogenous estrogen administration. Following FDA's publication of the DESI review results, no other indications could be legally promoted by Upjohn to United States physicians in its product insert, labeling, marketing, and promotions without first obtaining FDA's approval through an NDA submission. Simply stated, following the DESI review and FDA's publication of the results in the Federal Register, Upjohn should have ceased all promotion of Provera for use combined with estrogen in hormone therapy for menopausal females. Failure to do so was in direct contradiction to FDA's approved indications, and led to the inevitable result of physicians prescribing Provera for unapproved uses, to the potential harm of countless women.

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[4] Other examples include NDA-PRO 0029103, NDA-PRO 0029111-17, NDA-PRO 0029124-30; NDA-PRO 0029025-28, NDA-PRO 0029054-56, NDA-PRO 0001500-1509, NDA-PRO 0028888-28900

70. The DESI regulations speak to conflicts between prior pre-DESI marketing and post-DESI approved indications. The regulations require pharmaceutical companies to inform physicians of significant changes in the prescribing or promotional profile of a drug following the DESI review. (* Bold added for emphasis):

> **Sec. 201.200 Disclosure of drug efficacy study evaluations in labeling and advertising.**
>
> (3)(b)
>
> (1) The failure to disclose in the labeling of a drug and in other promotional material the conclusions of the Academy experts that a claim is "ineffective," "possibly effective," "probably effective," or "ineffective as a fixed combination," while labeling and promotional material bearing any such claim are being used, is a failure to disclose facts that are material in light of the representations made and causes the drug to be **misbranded**.
>
> (2) The Academy classification of a drug as other than "effective" for a claim for which such drug is recommended establishes that there is a material weight of opinion among qualified experts contrary to the representation made or suggested in the labeling, and **failure to reveal this fact** causes such labeling to be **misleading.**
>
> (g) The Commissioner may find circumstances are such that , while the elimination of claims evaluated as other than effective will generally eliminate the need for disclosure about such claims, there will be instances in which the **change in the prescribing or promotional profile of the drug is so substantial as to require a disclosure of the reason for the change** so that the purchaser or prescriber is **not misled by being left unaware through the sponsor's silence that a basic change has taken place**. The Food and Drug Administration will identify these situations in direct correspondence with the drug promoters, after which the **failure to make the disclosure will be regarded as misleading** and appropriate Action will be taken.

71. DESI and FDA did not approve Provera as effective for: opposing the effects of exogenous estrogen; providing a protective effect against the development of endometrial

hyperplasia; protecting against the development of cervical adenocarcinoma; or treatment of menopausal symptoms. Such claims of effectiveness, which had been promoted by Upjohn to physicians prior to DESI, were not permissible marketing claims after DESI. The DESI regulations clearly "required" that Upjohn inform physicians as to reasons for the change in marketing due to lack of support for "efficacy." It became Upjohn's responsibility, not the FDA's, to ensure its compliance with the Act in terms of marketing a "safe and effective" product to physicians after DESI which was not misbranded or adulterated.

Post-DESI Promotion of Provera for Use in Hormone Therapy

72. In 1975, researchers published data showing an association between the use of exogenous estrogen and endometrial cancer.[5] An Upjohn memo dated December 8, 1980 describes the impact on the estrogen market:

> Estrogen sales showed a substantial decline between 1975 and 1978, due largely to their being linked to an increased risk of endometrial cancer. Dollar sales for the category tumbled 20% over this time frame, with unit movement showing an even greater decline.
>
> Oral estrogens, currently representing 84% of the total estrogen market, have suffered sizable losses of late. The leading entry, Ayerst's Premarin, experienced a 30% dollar sales decline from 1975 and 1978. Its sales have leveled off at approximately $36 M per year. Currently Premarin accounts for 64% of the oral estrogen dollar sales.

NDA-PRO 000167.

73. In 1978, Dr. Robert Greenblatt published a paper in the Journal of the American Geriatrics Society finding that the risk of estrogen related uterine cancer could be avoided if progesterone was added to the regimen for menopausal women with an intact uterus.[6]

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[5] Ziel HK, Finkle WD. *Increased risk of endometrial carcinoma among users of conjugated estrogens*. N Engl J Med. 1975; 293(23): 1167-70.

74. This and similar publications not only saved estrogen therapy from extinction due to women's and physicians' concerns about increased cancer risk, but also, more importantly from Upjohn's perspective, presented a goldmine of opportunity. Upjohn executives recognized the market potential of Provera for use in opposing estrogen's negative health effects and physicians' and women's concerns about endometrial cancer risks. This is evidenced by an internal Upjohn document dated December 19, 1980. Significantly, the memo was written by Frank Fletcher, Domestic Pharmaceutical Sales, and addressed to all Sales Directors, Sales Managers, and District Managers. The letter states:

> "Forty-five percent of Premarin new prescriptions are written for 1 mg to 2 mg daily, with most of this segment written for 1.25 mg per day. At this level of drug administration, it can be assumed that endometrial hyperplasia may be even more prevalent among the perimenopausal population than anticipated. This further supports the opportunity which exists for Provera tablets." (Emphasis added).

NDA-PRO 0001166

75. On April 28, 1980 Dr. George Ishler, Upjohn Regulatory Affairs, wrote to FDA under the heading "LABELING FORMAT INSERT REVISION." The letter stated that Upjohn was supplementing its new drug application for Provera to provide for a revised package insert. The letter included a 1979 package insert along with copies of the proposed draft revised package insert. (NDA-PRO 0020242).

76. Upjohn's proposed draft revised package insert went beyond mere changes in format. The revised draft package insert attempted to expand Provera's indications to include use for menopausal women with dysfunctional bleeding secondary to administration of exogenous estrogen. Under the heading "Therapeutic Uses and the sub-

[6] J Am Geriatri Soc. 1978 Jan; 26(1):1-8

heading "Dysfunctional (anovulatory) bleeding in the reproductive-aged woman," Upjohn proposed adding the following:

> The prevention of dysfunctional bleeding induced by unopposed exogenous estrogen therapy for menopausal symptoms and the attendant potential risk of the unopposed estrogen to cause endometrial hyperplasia. NDA-PRO 0020252

And the following:

> The prevention of dysfunctional bleeding induced by unopposed exogenous estrogen therapy for menopausal symptoms and the attendant potential risk of the unopposed estrogen to cause endometrial hyperplasia. Dosage -- 5 my or 10 mg daily for 10 days should be given once per month or once every other month with progestogen withdrawal bleeding occurring in those women whose estrogen therapy has proliferated their endometrium.

NDA-PRO 0020257

77. An internal Upjohn memo written by Ken Hass dated September 20, 1984 describes FDA's decision on this supplemental application as follows:

> Specifically, the compliance reviewers asked for a retreat to the approved (1) box statement, (2) indications, (3) contraindications, and (4) adverse reactions. They asked that (1) the box be moved to the front, (2) the laboratory tests be moved to the drug interaction section, and (3) that overdose phenomena be described, if there are any. Perhaps most important, retreat to the wording of the old insert would remove our "unopposed estrogen" statement. (emphasis added)

NDA-PRO 0000200

78. Mr. Haas final sentence is significant for two reasons. First, it states that FDA refused to expand Provera's indications to include use to oppose estrogen in hormone therapy in menopausal women with dysfunctional bleeding. Second, that Mr. Haas' begins the sentence with "[p]erhaps most importantly." Clearly, the "unopposed estrogen" language and claim was important to Upjohn in the new revised draft labeling. The legality of their marketing campaign – Provera to oppose exogenous estrogen –

depended upon them having an approved indication for that use. It thus should have been clear to Upjohn, at least as of the date of this memo, that Provera's present approved indications did not include use in a combined hormone therapy in menopausal women to oppose the effects of dysfunctional bleeding and exogenous estrogen. This would be but the first of several attempts by Upjohn to obtain an alternative method to obtain an approved indication from FDA for Provera to oppose exogenous estrogen in combined hormone therapy without conducting well-controlled scientifically valid studies to support the safety and efficacy of combination use in menopausal and postmenopausal females.

79. In a letter dated October 27, 1981 to all sales personnel the writer, William Pentecost, describes an attached 1981 medical journal article entitled "Estradiol and Progesterone Receptors in the Estrogen-primed Endometrium."[7] According to Mr. Pentecost, the article "helps to establish the anti-estrogenic effect of progestins and supports the rationale of using progestin therapy to oppose unopposed estrogen." Further, he points out that "[t]he authors conclude from this study that cyclic progestin therapy seems to have a protective effect against the development of hyperplasia." (Kennally-W 0000147).

80. Also relevant is Upjohn's Corporate Product Statement for Provera, approved November 9, 1981 (RM_AA 0156179). This document reflects an emphasis on the use of Provera in hormone therapy. The following statements are illustrative:

> Provera is a progestational agent devoid of androgenic and estrogenic Activity. PROVERA in appropriate doses suppresses the secretion of the pituitary gonadotropins which, in turn, prevents follicular maturation, producing anovulation in the reproductive- aged women. This action may

[7] PJ Natrajan et al., #8891-91, published in the Am J Obstet Gynecol, 140(4):387-392, 1981

> also account for the ability of PROVERA to ameliorate vasomotor symptoms in the menopausal woman.
>
> PROVERA is also useful for the prevention of dysfunctional bleeding induced by unopposed exogenous estrogen therapy for menopausal symptoms and the attendant potential risk of the unopposed estrogen to cause endometrial hyperplasia.
>
> PROVERA is indicated: 1) for diagnostic use: primary and secondary amenorrhea; 2) for abnormal bleeding due to hormonal imbalance in the absence of organic pathology; 3) as an adjunct to estrogen therapy; 4) in the treatment of endometriosis; 5) as adjunctive and/or palliative treatment of recurrent and/or metastatic endometrial or renal carcinoma; and 6) in the treatment of hormonally—dependent, recurrent breast cancer in post—menopausal women.

81. Upjohn used the scientific hypothesis presented in the Greenblatt paper to seize the marketing opportunity presented by the endometrial cancer scare. Their strategy is plainly set forth in a series of documents entitled "Promotion Plan I." RM_NY_MOPS 0234095.

82. A 1982 Upjohn document entitled "Low Dose Provera Tablets Promotion Plan I" with the subheading "Sales Training Notes" describes the plan's intent as follows:

> Promotion Plan I is designed to promote Provera tablets at low dose (10 mg daily) as a first choice drug for various medical treatment problems associated with "unopposed" estrogen therapy.
>
> RM_NY_MOPS 0234095

The document further states:

> 2. BENEFITS OF PROGESTOGEN WHEN ADDED TO ERT
>
> Since 1975, there have been reports of several controlled studies of estrogen use and endometrial cancer involving thousands of patients with the disease. Almost all studies have indicated a positive association. The addition of a synthetic progestogen to ERT has been proved to be very beneficial in that it:

> - Helps control vaginal bleeding during continuous or cyclic estrogen therapy. In many cases, therapy with a progestogen can help to avoid repeated D&C's and unnecessary surgical intervention.
> - Reduces the risk of hyperplasia which may lead to endometrial cancer.
> - Reverts hyperplastic endometrium to normal or atrophic endometrium.
> - Helps patients receive and/or remain on ERT which may last up to several years.
> - Reduces cost of endometrial sampling, which is often recommended every six months in patients on cyclic administration of unopposed estrogen (sampling is recommended every two years in patients on ERT + progestogen).

And, significantly, the note that immediately follows the above states:

> You can support the discussion of these benefits with interested physicians with the attached reprint "Use of the Progestogen Challenge Test to Reduce the Risk of Endometrial Cancer" by R.D. Gambrell, et al.

As such, Upjohn's intention that its sales force promote Provera to the medical community for these uses is made clear.

83. A letter from Robert Heaps, Product Manager /Marketing Planning, Upjohn International Inc., dated August 25, 1982 (RM_NY_MOPS 0234089) and directed to recipients of Promotion Plan I provides evidence that Promotion Plan I was sent to international subsidiaries. The following statements from this letter are noteworthy:

> PROVERA Tablets Promotion Plan I discusses the "hidden risks" of unopposed estrogen therapy and the role of PROVERA Tablets in reducing these risks. The risks of unopposed estrogen therapy are documented for those physicians who are not aware of them while, for those who are, a rationale is provided for the use of PROVERA Tablets as opposed to other progestogens.
>
> This Promotion Plan will enable subsidiaries to promote PROVERA Tablets as an adjunct to estrogen replacement therapy for the treatment of menopausal symptoms.

84. While this letter sets forth a strategy for international sales, Upjohn's subsequent course of domestic promotion was consistent with Promotion Plan I.

85. The first of such efforts appears to be a lecture program entitled "Hormonal Therapy in the Menopause" having a copyright of 1982, The Upjohn Company. (NDA-PRO 0027938). The purpose of this lecture program is stated succinctly in the introduction:

> A reluctance to use estrogen replacement therapy can be directly related to the controversial link between estrogen and cancer of the endometrium. The utilization of a progestational agent to reverse the estrogen-induced hyperplasia can be viewed as a major breakthrough in the management of postmenopausal problems.

(emphasis added).

86. Additional evidence of Upjohn's efforts to establish itself within the hormone therapy market is found in a request for a product line extension written by Jim Penrose in October 1983. (RM_AA- 0156146-8). This document discussed the proposed development of a combination hormone therapy package containing both Provera 10mg and a conjugated estrogen. Significantly, the proposal described the history of progestin in menopausal hormone therapy as follows:

> In the mid 1970s, estrogen treatment of menopausal vasomotor symptoms lost favor because of an increased incidence of endometrial cancer which paralleled the increase in estrogen therapy use in the late 1960s and early 1970s. Within the last five years, studies by a number of prominent investigators (Speroff, Kase, Judd, Glass, Hirvonen, etc.) have shown that estrogen's tendency to produce endometrial hyperplasia, which sometimes leads to endometrial cancer, can be nullified by the periodic administration of a progestational agent which converts a proliferative endometrium to a secretive one, thus mimicking the normal menstrual cycle. The effect of these studies and the work of our MSL-RM&O and MSR groups has been to dramatically increase PROVERA sales from $6 million in 1980 to an anticipated $13—$14 million in 1983. It is estimated that 80—90% of these additional sales are due to the use of PROVERA in opposing estrogen therapy.

(emphasis added).

87. The significance of the above underlined statements is two-fold. The first

sentence attributes the anticipated doubling of Provera sales, in part, to the work of its MSL-RM&O, that is the Medical Sciences Liaison – Reproductive Medicine & Oncology, and MSR, that is the Medical Services Representative groups. When read in context with the entire passage, it is clear that Provera's dramatic increase in sales is due, in part, "to the work" of these groups within Upjohn promoting Provera for use in opposing estrogen in hormone therapy – an unapproved indication. The second sentence states that an estimated 80-90% of the increased sales are attributable to the use of Provera in opposing estrogen therapy. Thus, Upjohn expected to realize an 80-90% increase in Provera sales due, in part, "to its work" in promoting Provera off-label for use in opposing estrogen in hormone therapy.

88. Also noteworthy is the coversheet to this proposal (RM_AA 0156145). This document contains the names, signatures, and comments of the Upjohn executives that reviewed the proposal. Significant is the first comment by J.W. Greene, "This is a product our customers want. I strongly support it, but we do need to get an indication for menopause." (Emphasis in Original). This comment indicates that Upjohn knew Provera's existing indications did not extend to use in menopausal hormone therapy.

89. In furtherance of the goals outlined in Promotion Plan I, Upjohn disseminated a promotional advertisement in 1983 with the heading "The other half of estrogen replacement therapy," which claimed: "Provera opposes unopposed estrogen to reduce the likelihood of endometrial hyperplasia in menopausal patients." NDA-PRO 0027869

90. And again, in 1984 Upjohn published a promotional advertisement with the same heading, "The other half of estrogen replacement therapy," that made the following claims: "Unscheduled bleeding is associated with a high incidence of endometrial

hyperplasia;" and "Add Provera to control unscheduled bleeding and reverse endometrial hyperplasia." NDA-PRO 0027815 (emphasis added). Recognizing the commonplace use of estrogen therapy, Upjohn, without and FDA approved indication, overtly sought to ride the coattails of Ayerst's dominance of the exogenous estrogen replacement therapy market by promoting combination hormone therapy to physicians.

91. FDA issued its first protest to Upjohn by letter on January 5, 1984. (NDA-PRO 0017599). In this letter from the Division of Drug Advertising and Labeling to George Ishler of Upjohn, FDA refers to an advertisement for Provera that appeared in the December 1983 issue of Contemporary OBGYN. FDA requested "the immediate cancellation of this advertisement and any other advertisements or promotional labeling pieces which imply the use of Provera with estrogen replacement therapy except in those situations as described in your approved package insert." Importantly, FDA stated:

> We realize that the concurrent use of these treatments is becoming a more common practice among physicians. However, until your approved package insert has been change to reflect routine concurrent use, you are misbranding your product by promoting it for an unapproved indication.

92. Yet Upjohn ignored this warning. A year and a half later, the FDA issued a second warning letter dated September 10, 1985. (NDA-PRO 0011994). In this letter the Division of Drug Advertising and Labeling refers to a reprint submitted with form 2253 and an advertisement dated January 1985 entitled "The other half of estrogen replacement therapy." FDA writes:

> We request immediate cancellation of the advertisement and that you cease further dissemination of the reprint. Both of these promotional pieces present Provera as being safe and effective for the treatment and reversal of endometrial hyperplasia which is not an approved indication for your product.

RM_NY_MOPS 0103384 is a Provera advertisement bearing the heading "the other half of estrogen replacement therapy" and is dated March 1985. This is, presumably, the piece to which FDA refers above.

93. Upjohn persisted in its efforts to capture the physician menopausal hormone therapy market. A letter dated September 4, 1985 from George Ishler to FDA requests a meeting to discuss development of a combination estrogen- progestin package. (NDA-PRO 0070099). Dr. Ishler wrote:

> As you know, we currently market Provera for 'abnormal bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer.' We are considering the acquisition of a conjugated estrogen, which we wish to market in a package that appropriately sequences the estrogen plus Provera to address this complication of unopposed estrogen therapy experienced by what appears to be at least 28% of an estrogen-treated population of women.

94. Apparent from this letter, Upjohn took the position with FDA that its post-DESI indication for "abnormal uterine bleeding" in the absence of organic pathology included the use of Provera in the treatment of dysfunctional bleeding which had been associated with exogenous estrogen administration in menopausal females. Equally apparent, from the promotional material and internal memorandums described above, was that Upjohn anticipated Provera's use in hormone therapy would extend far beyond "at least 28% of an estrogen-treated population of women" and would be prescribed primarily for the prevention of endometrial hyperplasia and carcinoma due to unopposed exogenous estrogen.

95. Dr. Ishler's notes from the September 26, 1985 meeting with FDA reveal FDA's concern on the limits of Provera's indication for abnormal uterine bleeding. (RM_AA 0156196). He writes:

> Dr. Sobel questioned if we were basing approval of the product on an interpretation of the indication which was never intended by FDA. In other words, the present indication may originally been based on endogenous hormonal imbalance and not on exogenous hormonal imbalance. He said the agency would have to make a decision on this.

(Emphasis in original)

96. Another Upjohn Memo describing the September 26, 1985 meeting with FDA describes the discussion as follows (NDA-PRO 0000185):

> A meeting reported on by GHI in his trip report has some repercussions on promotion. Dr. Sobel charged Mr. Feather with remaining vigilant against the recommendation of PROVERA for the reversal of endometrial hyperplasia. Their argument was based on the fact that our indication was obtained using data from women who developed unscheduled bleeding without receiving exogenous estrogens. Use of the product in women on unopposed estrogen, may well require a new NDA. It seemed from this meeting that our current promotion, as worked out with Ms. Tyson, would remain intact but not on very solid ground.

(Emphasis added)

97. An Upjohn executive's handwritten notes from the meeting further clarifies FDA's position after Penrose's presentation on Upjohn's asserted rationale for a combination package – increased patient compliance. Dr. Sobel, FDA, responded "this is a new indication…[w]e are attempting to expand the existing indication…if we approve the NDA we are expanding the indication. It would have to go to office level. This would require an indication NDA." (Emphasis in Original) (NDA-PRO 0000186).

98. Upjohn's argument that Provera's present indications included use in opposing the effects of physician prescribed **"exogenous"** estrogens is further refuted by Provera's label entries published in the Physician's Desk Reference from 1975 forward. The section entitled "Actions" contained the following: "Medroxyprogesterone acetate, administered orally or parenterally in the recommended doses to women with adequate

"endogenous" estrogen, transforms proliferative into secretory endometrium." (emphasis added).

99. Upjohn's second attempt to obtain an indication for combined hormone therapy for Provera began with a letter from FDA dated April 4, 1986. (NDA DE 0000363). The FDA sent this letter to all estrogen manufacturers. As the sponsor of estrogen product NDAs 16-649 and 17-968, Upjohn received a copy of this letter. The letter requested that based on the Agency's safety concerns about prescribed exogenous estrogens, the following information be added to the INDICATIONS AND USAGE section of labeling for all estrogen-containing products:

> The lowest effective dose appropriate for the specific indication should be utilized. Studies of the addition of a progestin for seven or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia. Morphological and biochemical studies of endometrium suggest that 10 to 13 days of progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established. There are possible additional risks which may be associated with the inclusion of progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism. The choice of progestin and dosage may be important in minimizing these adverse effects."
> (The sentence which begins "The potential risks..." may be placed in the PRECAUTIONS section instead of this section.)

100. Upjohn responded with a letter to FDA dated July 8, 1986, referencing NDA 11-839 for Provera. (NDA-PRO 0011628). Upjohn wrote:

> We are supplementing our approved New Drug Application for the above to provide for a change in the package insert. It is our proposal to add the following as a second paragraph under Indications:
>
> "Addition of a progestin for seven or more days of a cycle of estrogen administration has been reported to lower the incidence of endometrial hyperplasia. Morphological and biochemical studies of endometrium suggest that 10 to 13 days of PROVERA administration are needed to

> provide maximal maturation of' the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established. There are possible additional risks which may be associated with the inclusion of progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism. The choice and dosage of progestin may be important in minimizing these effects."
>
> The changes mandated in estrogen labeling (letter attached) demand this complementary addition to progestin labeling, in providing definitive information as to dose and duration of therapy.
>
> The inconsistency now existing between progestin package inserts and estrogen package inserts is potential source of confusion to the practicing physician. We believe it is inappropriate to communicate important prescribing information concerning drug safety in one package insert (i.e. the estrogen insert), yet neglect to incorporate this message in the package insert of the drug class credited with providing that additional element of safety. Failure to address this issue in labeling will have far-reaching medical and legal implications.

101. On May 29, 1987 FDA requested all sponsors of progestin NDAs to add a similar statement to the PRECAUTIONS section of their labeling. (NDA-PRO 0011608). Upjohn responded with a letter dated July 1, 1987. Upjohn again seized the opportunity to argue for the addition of a new "indication" in Provera's labeling when it wrote:

> In response to your letter of May 9, 1987, regarding a suggested statement to be added to the labeling for PROVERA Tablets (medroxyprogesterone acetate tablets, USP), we have several comments and concerns.
>
> In considering our response, we reviewed the Agency's letter of April 4, 1986, requesting manufacturers of estrogens to amend product labeling with the addition of the following section to the INDICATIONS AND USAGE section:
>
> "The lowest effective dose appropriate for the specific indication should be utilized. Studies of the addition of a progestin for seven or more days of a cycle of estrogen administration hive reported a lowered incidence of endometrial hyperplasia. Morphological and biochemical studies of endometrium suggest that 10 to 13 days of progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has no been clearly established. There are possible additional risks which

> may be associated with the inclusion of progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism, The choice of progestin and dosage may be important in minimizing these adverse effects."
>
> We complied with this request and anticipated that a similar statement would appropriately be added to the INDICATIONS AND USAGE section of progestin labeling, ie, PROVERA (medroxyprogesterone acetate tablets.
> USP).
>
> This situation, viz suggested indication for the use of progestin in the estrogen labeling while no such indication exists in the progestin labeling, has posed a medico-legal dilemma for both manufacturers and practitioners.

NDA-PRO 0011591
(Emphasis added).

102. Again, Upjohn attempted to obtain what the FDA considered a new indication for Provera without conducting any studies into support the safety and efficacy of combination hormone therapy. This matter appears to have been resolved on October 25, 1989 when Upjohn wrote FDA attaching a draft copy of the Provera insert," revised to add a paragraph on addition of a progestin to an estrogen replacement regimen, under PRECAUTIONS." (NDA-PRO 0002106). Thus FDA, once again, refused to permit Upjohn a new indication for use of Provera with exogenous estrogen in menopausal hormone therapy. Significantly, the updated Provera package insert did not appear in the PDR until 1993.

103. On April 7, 1986 Upjohn filed a supplemental NDA (S-048) in another attempt to obtain FDA's approval for the "use of Provera to oppose the endometrial effects of estrogen in menopausal women receiving estrogen replacement therapy." In support of its supplemental NDA, Upjohn submitted 47 published journal articles and no testing or clinical studies that it had conducted. (NDA-PRO 0007648).

104. FDA denied S-048 on January 15, 1988 finding "only four of the 47 articles submitted involve long-term studies with supplemental MPA." Further, the four articles which contained long-term studies with MPA had deficiencies considered by FDA substantial enough to render the application as "not approvable". (NDA-PRO 0007648). In short, Upjohn had provided no adequate science or clinical studies for support of safety and efficacy of long-term MPA use in conjunction with estrogen therapy in menopausal women.

105. FDA's third denial of Upjohn's request for a hormone therapy indication was, apparently, no deterrent to Upjohn's efforts to promote Provera to physicians for that unapproved indication. Additional evidence of such promotion can be found in the brochure entitled, "Current Medical Topics: Management of the Menopausal Patient." This brochure is copyrighted 1988, The Upjohn Company. (RM_NY_MOPS 0102637). While it contains the disclaimer that the opinions and recommendations expressed therein are those of the authors and not necessarily those of The Upjohn Company, it is clear that Upjohn funded its publication. Further, the marketing purposes behind its publication are apparent given the documents described above setting forth Upjohn's history of promoting Provera to physicians for prescription for off-label uses in hormone replacement therapy.

106. Yet further evidence can be seen in an Upjohn memoranda of December 1989 entitled "Sales Information Notes." (RM_NY_MOPS 0234458). While the cover page is stamped "For your education: This is not to be shown to physicians or other customers," the document is intended to train sales agents about use of the product to continue to promote unapproved use to physicians. Indeed, the document virtually instructs the sales

representative to "discuss" the recommended unapproved therapy with physicians. The introductory paragraph states the purpose of the document to be as follows:

> These sales notes are intended to provide you with some basic information on menopause, to discuss current recommended therapies, and to look at new areas of interest as they pertain to the treatment of menopause with combination estrogen-Provera therapy.

107. Apparently aware that Provera continued to lack an indication to oppose exogenous estrogen in menopausal women, there are communications between Upjohn and FDA in 1989 regarding Upjohn's proposed clinical study protocol to support approval of an NDA Supplement for such a new indication.

108. On May 26, 1989, FDA's Tie-Hua Ng, PhD, Mathematical Statistician, issued a Statistical Review and Evaluation of Upjohn's proposed protocol to support the approval of a new indication for use of Provera in the prevention of endometrial hyperplasia for women on estrogen therapy. (NDA-PRO 0007375-9). The FDA strongly objected to Upjohn's proposal to limit enrollment to a study population to only females with hysterectomies. The study design proposed would be unable to address endometrial hyperplasia. Instead, Upjohn had proposed a study of lipid profiles in hysterectomized population receiving combination estrogen and Provera. The FDA concluded that the study would only be able to address lipid levels in postmenopausal women with hysterectomies receiving combination estrogen and Provera versus estrogen alone therapy – not whether the addition of a progestin prevented endometrial hyperplasia. FDA recommended the sponsor reconsider the design of the study.

109. In a September 14, 1989 letter, Upjohn disagreed with the FDA's comments regarding the problems with its proposed clinical study design. (NDA-PRO 0007222).

Upjohn subsequently halted the study due to technical problems - the failure of the Conjugated Estrogen Tablet selected by Upjohn to meet USP requirements for content uniformity. (NDA-PRO 0007227).

110. Upjohn continued to promote Provera to physicians for use in hormone therapy. An example of this promotion to physicians is a publication entitled "Issues in Menopausal Hormone Therapy," copyright 1990, The Upjohn Company. (NDA-PRO 0027456). This document discussed the "short-term and long-term advantages of hormone therapy." Included among the "advantages" are the treatment of vasomotor symptoms, urogenital problems, osteoporosis, and cardiovascular disease. The brochure promotes Provera's off-label indication to oppose exogenous estrogen to prevent endometrial hyperplasia. **It further makes the claims that Provera would not have a detrimental effects on the lipid benefits of estrogen and "the addition of a progesterone to menopausal therapy had no detrimental effects on estrogen's benefits for osteoporosis."** The message which was to be sent to physicians was that CHT (combined hormone therapy- Provera + estrogen) is "cardio-protective", just like estrogen. The study cited, was a 12 week trial of CHT. Under the section, "Cardiovascular Risks," the subject of the effect of CHT is avoided, but rather there is mention that some data exists showing that "estrogen" can reverse negative lipoprotein patterns. Importantly, neither "estrogen only" hormone therapy nor CHT was ever approved by the FDA for the prevention of "cardiovascular diseases".

111. Perhaps most disturbing about this brochure is that Upjohn was promoting to physicians that Provera as having no detrimental effects on the lipid benefits of estrogen. This promotion to physicians occurs four years after the FDA requested Upjohn to

update Provera's package insert to include a statement in the precautions section that, among other things, "There are possible additional risks which may be associated with the addition of a progestin…potential risks include adverse effects on …lipid metabolism." (NDA-PRO 0011608). Further, this brochure appeared three years after Upjohn had complied with the FDA's request to change the labeling by submitting a supplemental NDA, but three years before that new precautions statement would actually appear in Provera's PDR product insert information.

112. A further example of Upjohn's promotion in 1990 to physicians is a promotional advertisement entitled "In menopausal Hormone Therapy - When unscheduled bleeding occurs with estrogen…make Provera the other half of HRT." (NDA-PRO 0027466). Again, this is yet another instance of Upjohn's riding the coattails of the estrogen hormone therapy market. These "efforts" to promote to physicians were clearly successful commercially. By 1991, Provera was ranked #34 of 100 prescription drugs in terms of new prescriptions and Premarin was # 7. Also in 1991, Provera was ranked #27 and Premarin was 1st in terms of refills (all strengths). (Exhibit 19, John Ryan Deposition).

113. In 1990, the Division of Drug Advertising and Labeling issued a series of warning letters to Upjohn in response to its unapproved promotion of Provera to physicians. The first is dated October 9, 1990. In this letter FDA refers to a reprint entitled "Estrogen Replacement Therapy A Survey of Women's Knowledge and Attitudes." Having reviewed the content of the article, FDA writes:

> Provera tablets are **NOT** indicated for combination estrogen and progestin therapy in ERT to reduce the risks of postmenopausal osteoporosis.

> If, in fact, this reprint was issued July 1990, such labeling would have misbranded your prescription drug product Provera Tablets under Section 502(f) of the Act.

NDA-PRO 0002030

(Emphasis Original)

114. The second warning letter is dated October 16, 1990 (NDA-PRO 0002026) and refers to an "advertisement for Provera (medroxyprogesterone acetate) Tablets advocating their use in menopausal therapy as 'the other half of hormone replacement therapy.' (Emphasis original). FDA further states "[t]here are no estrogen products approved for use with Provera in the treatment or prevention of postmenopausal symptoms."

115. Notably, five years previously Upjohn had been cautioned for an advertisement entitled "The other half of estrogen replacement therapy." (NDA-PRO 0011994). To continue this line of promotion after repeated warnings, and after being denied on three occasions an indication for use in menopausal hormone therapy by FDA, reflects a total disregard for the role of FDA to protect the public health and the regulations pertaining to the marketing of pharmaceutical products in the United States.

116. A third letter from FDA's Division of Drug Advertising and Labeling is dated October 30, 1990. (NDA-PRO 0002021). This letter refers to a meeting between representatives from Upjohn and FDA following the two prior warning letters. FDA writes:

> You and the other Upjohn representatives denied that Upjohn was trying to capture the postmenopausal Hormone Replacement Therapy (HRT) market and contended that Upjohn was promoting the drug strictly with the approved indications for use, i.e., for the treatment of **abnormal bleeding due to hormonal imbalance**. (emphasis original)

FDA further writes:

> Subsequent to the meeting, your contention that Upjohn is not trying to capture the postmenopausal HRT market was [further] refuted by several pieces of promotional labeling received October 19, 1990 by this Division with a Form FDA 2253 dated September 18, 1990 and submitted to NDA 11-839, PROVERA (medroxyprogesterone acetate) Tablets. In addition, a mailer and BRC (USD—3728.00 September 1990) promoting PROVERA CPTM Tablets (medroxyprogesterone acetate) 2.5 mg Convenience Pack was recently received with a "Dear Doctor" letter (USD3730.00) signed by Sharon L. Roehl, Product Manager. In addition to repeating the previously discussed claim "In menopausal therapy. . . PROVERA can provide the other half of hormone replacement therapy (HRT)," the letter refers to the subject of our October 9, 1990 letter to you concerning the reprint, 3353 (Ferguson) issued 7/90, as follows:
>
> "A January 1989 study in Archives of Internal Medicine noted that women may be reluctant to take long—term HRT because they think it is inconvenient."
>
> "With that in mind, we'd like to introduce you to the new Convenience Pack of PROVERA CPTM Tablets(medroxyprogesterone acetate) 2.5 mg."
>
> "When you choose PROVERA, the Convenience Pack provides a unique alternative for your patients. Each package of PROVERA CP Tablets contains twenty-eight 2.5 mg PROVERA Tablets."
>
> "As you are well aware, convenience can mean the difference between faithfully following a course of therapy or letting it fall by the wayside..." Ferguson. . .
>
> The mailer pictures the PROVERA CP Tablets (medroxyprogesterone acetate) 2.5 mg Convenience Pack which also contains the headline: "Provera...the other half of hormone replacement therapy...."
>
> All of the above cited promotional materials fall within our previous requests that Upjohn take immediate steps to halt all reprints and all advertisements or promotional labeling pieces which may make identical or similar representations or suggestions for unapproved use(s) of the product.

117. The blister pack referenced above refers to Upjohn's supplemental NDA S-055. This application was submitted November 9, 1989 and approved by FDA on July 5,

1990. The application sought approval for the packaging of Provera Tablets 2.5 mg in a PVC blister pack. On October 30, 1990 FDA's Dr. Sobel sends a letter to Upjohn stating:

> It has just come to our attention that you are marketing this product in a blister package which you term a "Convenience Pack" containing twenty-eight 2.5 mg Provera tablets. Your promotional material concerning this "Convenience Pack" indicates that it is to be used for menopausal hormone replacement therapy, an unapproved indication.
>
> Your supplemental application did not indicate your intention to package the product in units of twenty-eight tablets. Further, it was not our intent to approve a blister package containing this number of tablets nor to approve any package for an unapproved indication.
> NDA-PRO 0002025

118. A chronology of events relating to the 28-day blister pack can be found at CHIRBY-D 0000952. A Dear Doctor letter announcing the availability of the blister pack can be found at NDA-PRO 0002012, and an advertisement for the package at NDA-PRO 0027444. Upjohn announced its withdrawal of the blister pack by letter to the FDA dated November 9, 1990. NDA-PRO 0002006. Upjohn informed physicians of the product's withdrawal by letter dated March 1991. Chirby-D 0000992. FDA published notice of the withdrawal in the Federal Register on October 18, 1991 at 56 FR 52272. The events surrounding the 28-day blister pack became the subject of an FDA investigation. (Breed K- 0007327).

119. This regulatory history provides conclusive evidence of Upjohn's persistence in promoting Provera to physicians for use in menopausal hormone therapy despite repeated FDA warnings, meeting and letters. Further, it suggests a disregard and manipulation of the regulatory process in that Upjohn omitted to include in the NDA Supplement the number of tablets, 28, contained in the blister package, a material fact that clearly would

have impacted on FDA's approval decision. Chirby-D 0000931. From their prior history dealing with FDA over this issue and the speed of the follow-up response of FDA , Upjohn knew or should have known that the NDA supplement would not have been approved had the number of tablets intended for the blister pack been disclosed to FDA's reviewers.

120. Two additional letters from FDA's Division of Drug Marketing, Advertising and Communications followed the withdrawal of the 28-day blister pack. Both related to promotional pieces Upjohn sent to FDA to obtain its comments before publication. These letters are significant, again, because they demonstrate Upjohn's unrelenting persistence in promoting Provera to physicians for unapproved use in hormone therapy in menopausal/postmenopausal women. The first dated November 13, 1990 refers, among other things, to four journal article reprints and states:

> Unacceptable – if Upjohn wishes to promote the drug for Hormone Replacement Therapy (HRT) in menopausal/postmenopausal women, the proper way to do it is to gather the evidence and submit a supplemental New Drug Application to obtain an indication for such use in the approved product labeling.
> NDA-PRO 0002003

The second letter, dated December 9, 1991 refers to a proposed detail presenter and journal ad for Provera. FDA states:

> To include a post menopausal patient as a potential candidate for treatment with Provera is not recommended. This is potentially misleading to the reader regarding the indications for use of the product.
> NDA-PRO 0027233

121. Upjohn's Dr. Philander wrote an interoffice memorandum regarding a November 6, 1990 meeting with DMEDP to discuss the "dilemma in which the practicing physician has been placed" by labeling for estrogens which stated under "PRECAUTIONS" that a

progestational agent should be used in conjunction with estrogen therapy. At the same time, there is no labeling for any progestin for use in this situation. He asserted this situation has created **confusion** and has generated numerous inquiries from physicians as to the recommended dose of PROVERA for this indication. (Chirby-D-0001022). In other words, Dr. Philander suggests to FDA that based on what he views as physician confusion created by FDA, Dr. Sobel and the FDA should disregard the requirements of the Act and the need for valid scientific evidence supporting safety and efficacy, to address "physician confusion" by expanding Provera's indications to include information regarding use in opposing estrogen. In fact, the "physician confusion" and the "dilemma" to which Dr. Philander refers was entirely the result of Upjohn's violative promotion of combination therapy to physicians and failure to conduct well-designed clinical studies to support approval of a supplemental NDA for the indication.

122. Provera's financial importance to Upjohn is reflected in an internal newsletter entitled "The Provera Press," dated February 1991. Exhibit 16, Roehl Depo. In this newsletter to the sales force, Ms. Roehl writes, "Provera ended 1991 as the number 6 product in terms of total sales for the corporation, but it was number 1 in terms of profitability (as % of sales)." Also noteworthy are the following excerpts:

> Under the heading Medical Correspondence- "The continuous administration of Provera tablets versus the cyclic administration continues to be the most frequently asked question."
>
> Under the heading Sales Training – "Question - is an endometrial biopsy necessary before initiating hormone replacement therapy?"
>
> Sales Training Question - What are the major side effects of progestogens? Answer: "...Low dose continuous therapy decreases the risk of side effects compared to sequential therapy."

> What's the market doing section - "Over 70% of Provera use is for diseases of the genito-urinary system. The primary use being concomitant therapy with estrogen in the treatment of symptoms associated with menopause."

123. A 1993 document entitled "Strategy and Tactics" lists as a strategy "Increase physicians' awareness through increased detail activity and NSP to targeted audiences of FP/GPs and internists who are high prescribers of estrogen, as well as OB/GYNs." (emphasis added). (RM_NY_MOPS 0102854). Among the items listed under the heading Marketing/Sales Tactics is the following:

> An unrestricted educational grant is being provided to the National Osteoporosis Foundation and the American Medical Women's Association for the development of ongoing osteoporosis educational programs. These programs will be accredited for continuing medical education credits. Educational support is also being provided to the American College of Obstetricians and Gynecologists, as well as the North American Menopause Society.

124. Also in 1993, Upjohn set out, once again, to circumvent the regulatory requirements requiring a showing of proof of safety and efficacy for obtaining a new indication by attempting to exert external pressure on the FDA into expanding Provera's indications to include use in CHT. (RM_AA-0154204).

125. Upjohn's saw an opportunity to exert pressure on the FDA presented by FDA's "off-label use initiative" announced by letter dated April 27, 1993 sent to ten medical and professional organizations. (RM_AA-0154207). A list of the ten organizations can be found at RM_AA-0154240. FDA requested these organizations "provide a list in priority order of unlabeled drug uses considered most important and that have at least potential support in the literature and in unpublished data." (RM_AA-0154205). FDA's Commissioner Dr. Kessler indicted he wanted to "encourage" manufacturers to submit

marketing applications to obtain FDA approval of these unapproved indications and return to compliance with the Act.

126. Upjohn's misinterpretation as to the "purpose" of FDA's Drug Off-Label Use Task Force initiative was stated in an interoffice memo in which it was written "Last year Kessler and several other CDER officials were touting this initiative suggesting the agency might be willing to increase its reliance on literature reports in approving off-label uses." (RM_AA-0154206).

127. In response, Upjohn planned to "try encourage organizations to write the FDA re: hormone replacement therapy." An interoffice memorandum dated June 17, 1993 contains the following:

> Because of the timeframe the FDA has set for these organizations to respond, it is important that you make these calls by July 2 and request that the organizations respond by July 15, 1993 if at all possible.
>
> The following materials are supplied for your presentation:
>
> 1. Suggested outline to follow – worked successfully with AAFP – tailor to your individual client (RM_AA-0154219 – RM_AA-0154225)
>
> 2. Organization chart with contact person
>
> 3. April 27 letter from FDA to ten professional, medical, and pharmacy organizations
>
> 4. Provera section from three compendia recognized by FDA to indicate appropriate drug use:
>
> - U.S.P
> - AMA Drug Evaluation
> - AHFS/ASHP
>
> 5. Pink Sheet/Washington Drug Letter (RM_AA-0154241)
>
> 6. IMS Market Data
>
> 7. National Osteoporosis Guidelines for ERT

8. Premarin Package Insert

9. Provera/Menopausal Bibliography

10. Provera Reprint Notebook

11. List of drugs with most extensive frequency of off-label use

12. Provera package insert

13. ACP HRT Guidelines

RM_AA-0154217

128. Upjohn company documents establish that the plan was, in fact, set motion. RM_AA-0154227 is a chart detailing Upjohn's contact with 15 medical and professional organizations about Provera. Further, one interoffice memo states: "I have confirmed that the National Osteoporosis Foundation has sent the FDA a letter requesting a change in the package insert indications for MPA." (RM_AA-0154216). Examples of this and other letters sent to FDA at Upjohn's request can be found at RM_AA-0154229 – 36. Upjohn sought to contact these organizations and solicit letters be written from them to the FDA in order to exert pressure on the FDA to approve a new indication for Provera to oppose estrogen without requiring Upjohn to undertake the time and expense of designing and conducting clinical trials to ascertain Provera's safety and efficacy for this use as well as to "legitimize" Upjohn's continued marketing of Provera to physicians for that purpose.

129. Further evidence of Upjohn's persistent off-label promotion of Provera to physicians is an undated document, presumably from 1995, entitled "Prempro and Premphase Sales Notes." (RM_NY_MOPS 0168668). This document describes the recently approved CHT products and sets forth for its sales force "possible defenses" to

this competition. Among those defenses are "The fixed dosages of these combination packages limits the flexibility the physician has to individualize therapy for his/her patients…the market leader of progestins is Provera…Cycrin is a branded generic of Provera…Provera was used in the PEPI trial…No new medical advantage."

130. In 1996, "Pharmacia & Upjohn" assumed the sponsorship of the NDA for Provera.

131. September 2, 1997 (NDA-PRO 0002167) Pharmacia & Upjohn submitted Efficacy Supplement **S-068**. It requested FDA's approval of an NDA Efficacy Supplement supporting use of Provera for 12-14 days each month in combination with continuous conjugated estrogen replacement (CE 0.635 mg) for prevention of estrogen induced endometrial hyperplasia and endometrial carcinoma in nonhysterectomized post-menopausal women. Provera was to be used for 12-14 days each month in combination with continuous estrogen replacement. The primary support for efficacy provided were two published clinical trials and no actual clinical studies conducted by the sponsor: 1) a pivotal Phase III clinical trial, the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial which was sponsored by the National Institutes of Health (NIH) under a research project cooperative agreement; and 2) a supportive prospective 1-year, double-blind, randomized, multicenter study, the Menopause Study Group conducted at 99 sites in the United States and Europe by Johns Hopkins Hospital and Wyeth-Ayerst Research. Upjohn also submitted additional supporting information January 8, June 29, July 22 and August 3, 1998 to the Supplement. (* The FDA's User Fee Goal (Prescription Drug User Fee Act of 1992- PDUFA) had a mandatory deadline for completion of the application as **August 4, 1998,** which happened to also be the day that the Agency's approval letter for

the supplement was generated.) However, FDA approved a modified new indication for Provera NDA supplement.

132. The Medical Officer review began by discussing the use of unopposed estrogen therapy and the substantial numbers of postmenopausal women who had obtained relief of menopause symptoms for over 50 years with estrogen therapy, and more recently to prevent bone loss and fracture. It has been known since the early 1970s that unopposed estrogen use may increase the incidence of endometrial hyperplasia and cancer. Since the early 1990s, combined estrogen-progestin therapy had become more common as a regimen to relieve menopausal symptoms, delay bone loss and reduce the risk of estrogen-alone induced endometrial hyperplasia and cancer.

133. Both studies have an arm with continuous MPA, an indication not requested by Pharmacia Upjohn. The sponsor did not provide FDA with information as to why the continuous MPA was not requested for review in the NDA. The sponsor requested the following recommended dose: 1) 10mg given for 12-14 consecutive days/cycle or; 2) 5mg given 14 consecutive days/cycle (NDA 11-839/S-068, Volume 70.1, page 40). In addition, the Committee in Gynecological Practice of the American College of Obstetrician and Gynecologist concluded "that when medroxyprogesterone is used for hormone replacement therapy, 5.0mg should be the standard dose for the cyclic regimen (except for women with persistent heavy withdrawal menses) and 2.5 mg for the continues combined regimen.

134. On August 4, 1998 FDA sent Pharmacia & Upjohn notice that the agency had concluded its review and concluded that adequate information had been provided to support that the Provera drug product is safe and effective for use as recommended in the

agreed upon labeling. (NDA-PRO 0001545). Provera was now approved as indicated in "combination with continuous conjugated estrogen replacement (CE 0.635 mg) for prevention of estrogen induced endometrial hyperplasia in post-menopausal women." The FDA did not have sufficient evidence in the data to also indicate Provera for the new claim for reduction in endometrial cancer.

135. An early indication of a possible increased risk of breast cancer in combination hormone therapy was a French 1961 publication of an animal study involving a model using male rats as a hormone model for menopausal women receiving estrogen and progesterone in combination or separately.[8] In this study, the researchers found that the combination of estrogen and progesterone in rats produced adverse mammary effects while the administration of either estrogen or progesterone alone did not.

136. In 1976 a study appeared in the New England Journal of Medicine finding that the Relative Risk (RR) of breast cancer occurring in a population of women taking conjugated estrogens increased with length of follow-up compared to a similar population of women not receiving exogenous estrogens, and after 15 years the RR was 2.0.[9] Four years later, 1980, a case controlled study evaluating the effect of menopausal exogenous estrogen therapy on the risk of breast cancer estimated the RR for a total cumulative dose of 1500 mg to be 2.5. (Ross et al., 1980). Another study published the same year found that women taking exogenous estrogens after natural menopause were 3.4 times more like to develop breast cancer than nonusers or those who had undergone surgical menopause.[10]

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[8] Riviere M.R., Chouroulinkov I., Guerin M., *Appearance of mammary tumors in the male rat subjected to a combination treatment of estrogen and progesterone*, Societe De Biologie, Nov. 18, 1961; 2102-04.
[9] Hoover et al., *Menopausal estrogens and breast cancer*, NEJM 1976 Aug. 19: 295(8): 401-5.
[10] Jick et al., *Replacement estrogens and breast cancer*, Amer J Epi. 1980: 112(5):586-94.

137. In **1987**, the IARC listed estrogen as a human carcinogen and published an evaluation of medroxyprogesterone acetate (MPA) finding sufficient evidence existed of its carcinogenicity in animals, and further finding it was "possibly carcinogenic to humans." A 1988 review by Key and Pike on the role of hormonal factors in the causation of breast cancer suggested a hypothesis that combination hormone therapy may carry a greater risk of breast cancer than estrogen only hormone therapy.[11] Also in 1998, an article published in the International Journal of Cancer reported a RR of breast cancer in 1.36 for sequential therapy of estrogen and progestagen.[12] The following year, a study published in the New England Journal of Medicine reported a RR of 4.4 for breast cancer in Swedish women using combination estrogen and progesterone for more than six years.[13] A 1992 follow-up study reported that the increased risk of breast cancer associated with unopposed estrogen persisted, while the increased risk associated with combination estrogen and progesterone increased.[14] Also in 1992, G. Colditz et al. reported a relative risk (RR) of 1.42 of breast cancer in women using estrogen alone and a 1.54 RR for those using combination estrogen plus progestin.[15] The authors concluded that the addition of a progesterone does not remove the increased risk of breast cancer observed with current use of estrogen. The FDA's 1994 review of the Prempro NDA noted 6 cases of breast cancer, all in patients receiving combination therapy. (W-MDL303-00083745). This prompted the concern that "concomitant progestin may

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[11] Key, TJ, *The role of oestrogens and progestagens in the epidemiology and prevention of breast cancer*, Eur J Clin Oncol. 1988 Jan;24(1):29-43.
[12] Erwertz, M., *Influence of non-contraceptive exogenous and endogenous sex hormones on breast cancer risk in Denmark*, Intl J. Cancer: 42, 832-838 (1998).
[13] Bergkvist et al., *The risk of breast cancer after estrogen and estrogen-progestin replacement*, N Engl J Med. 1989 Aug. 3;321(5)293-7; Kennally-W 0000045
[14] Persson et al,, *Combined oestrogen-progestogen replacement and breast cancer risk.* The Lancet. 1992 Oct. 24. 340: 1044.
[15] Colditz, et al., *Type of postmenopausal hormone use and the risk of breast cancer: 12-year follow up from the Nurses' Health Study*, Cancer Causes Control.1992:3:433-9.

exacerbate the increased breast cancer risk reported with prolonged unopposed estrogen." Later observational studies also reported an increased risk of breast cancer with combination hormone therapy.[16]

138. The Women's Health Initiative Randomized Controlled Trial was designed in 1991-1992. The primary outcome of the estrogen plus progestin trial was to be coronary heart disease (CHD). The occurrence of hip fracture was considered a secondary outcome. Invasive breast cancer was considered a primary adverse outcome based on observational data. Additional clinical outcomes that may be affected by HRT included other cardiovascular disease, endometrial, colorectal, and other cancer and other fracture.

139. The design and conduct of the WHI trial was to examine the effect of hormone therapy on women's overall health and well-being. In an attempt to summarize important aspects of health v risk, a global index was defined as the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other causes. The WHI is the first randomized trial to directly address whether estrogen plus progestin has a favorable or unfavorable effect on CHD incidence and on overall risk and benefits in predominantly health women.

140. Eligibility was defined as women 50 to 79 years, postmenopausal, likelihood of residence in the same area for 3 years. Subjects were recruited from 40 US clinical centers in 1993-1998. The planned trial was to extend through 8.5 years. There was a 3-month wash-out period before baseline evaluation of women using postmenopausal

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[16] Colditz, G.A. et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med. 332, 1589-1593 (1995).
Schairer, C. et al. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA 283, 485-91 (2000).
Ross, R.K., et al. Effect of hormone replacement therapy on breast cancer: estrogen versus estrogen plus progestin. JNCI 92, 328-32 (2000).
Newcomb, P.A. et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. Cancer Epidemiol Bio Prevention 11, 593-600 (2002).

hormones at screening. Women with a uterus still present were eligible for estrogen plus progestin and women without a uterus for estrogen only. The 2002 report released in JAMA described 16,608 women with an intact uterus at baseline enrolled and randomized to receive placebo or estrogen plus progestin (0.625mg CEE and 2.5mg MPA (Prempro)). Of the 8506 assigned to the combination arm, as of April 2002, 7968 were still alive with data available through 18 months, 307 unknown status, and 231 deceased. Of the 8102 assigned to the placebo arm, 7608 were alive with data through 18 months, 276 unknown vital status, and 218 deceased.

141. On May 31, 2002, after a mean of 5.2 years follow-up, the Data and Safety Monitoring Board recommended stopping the trial of estrogen plus progestin v placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported that the risks exceed benefits. Estimated hazard ratios (HRS) were as follows: CHD 1.29 (1.02-1.63) with 286 cases, breast cancer 1.26(1.0-1.59) with 290 cases, stroke 1.41 (1.07-1.85) with 21`2 cases; PE 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83(0.47-1.47) with 47 cases; hip fracture, 0.66(0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Absolute excess risks per 10000 person years attributable to estrogen progestin were 7 more for CHD events, 8 more for strokes, 8 more for PEs and 8 more for invasive breast cancers, while the absolute risk reductions (benefits) per 10000 person-years were 6 fewer colorectal cancer and 5 fewer hip fractures. The absolute excess of risk of events included in the global index was "19 per 10000 person-years".

142. The conclusion of the WHI was that the overall health risks exceeded benefits from use of combined estrogen plus progestin at an average 5.2 year follow-up among healthy postmenopausal US women enrolled in the study. The risk-benefit profile found in this trial was concluded not to be consistent with the requirements for a viable intervention for primary prevention of chronic diseases. The WHI results indicated to the writing group that this regimen should not be initiated or continued for primary prevention of CHD, the primary endpoint for the study design.

Woman's Health Initaitive (WHI) and CANCER RISK:

143. The WHI interim results were further confirmation of the earlier medical literature and animal studies that combined estrogen plus progestin increased the risk of incident breast cancer. The WHI was a government funded study, neither Pharmacia & Upjohn nor Wyeth had previously examined the long-term risk of breast cancer in combination hormone therapy use. The WHI by its design, though limited in specific answers for breast cancer due to study size and design, still was able to provide an important signal not previously sought to be addressed or monitored by Pharmacia & Upjohn.

144. The WHI could not address the risk of death due to invasive breast cancer because of the relatively short follow-up time, few women in the WHI have thus far died as a result of breast cancer (3 in the active treatment group and 2 in the placebo group). The increased risk of breast cancer began to emerge several years after randomization. After an average follow-up of about 5 years, the adverse effect on breast cancer had crossed the monitoring boundary. The 26% excess of breast cancer in the combined treatment arm is consistent with estimates from pooled epidemiological data, which reported a 15%

increase for estrogen plus progestin use in breast cancer for less than 5 years and a 53% increase for use for more than 5 years. It is also consistent with the (statistically nonsignificant) 27% increase found after 6.8 years of follow-up in HERS.

145. On November 14, 2002 Pharmacia & Upjohn's Dan Chirby, Senior Regulatory Manager, submitted a prior-approval labeling supplement to FDA proposing changes in its physician insert and patient package for PROVERA. The changes proposed were in response to the recently published Women's Health Initiative (WHI) and the Heart and Estrogen/Progestin Replacement (HERS/HERS II) studies. He wrote that:

> The PREMPRO (0.625 mg conjugated equine estrogens (CEE) plus continuous 2.5mg medroxyprogesterone acetate (MPA) subset of the WHI study was stopped early due to an increased risk of breast cancer and cardiovascular events seen at year 5 in the study. Although not specifically used in the WHI study, PROVERA Tablets (MPA 5mg and 10mg) are currently approved for use as combination with CEE, but only in a sequential (cyclical) regimen. Pharmacia nevertheless believes it is important to communicate the implications of the WHI study results to healthcare providers who prescribe PROVERA in combination with PREMARIN (CEE) or other estrogens.
>
> Pharmacia has not conducted randomized clinical studies with PROVERA Tablets with a sample size or duration of treatment as large as that achieved in the WHI study, so we are unable to compare our clinical study data against the WHI data and conclusion. Pharmacia does maintain a spontaneous reporting systems (SRS) containing unsolicited adverse event reports. The primary purpose of the SRS is to serve as a signal alerting system…..The labeling changes being proposed for PROVERA Tablets are therefore derived exclusively by extrapolation from the published WHI and HERS data, and not from any Pharmacia clinical study or SRS database.

146. In his report entitled *Overall benefits and harms of combination hormone replacement therapy*, epidemiologist Graham A. Colditz summarizes the long and short-term benefits and risks of CHT as well as their degree of association. According to Dr. Colditz, the short-term risks associated with CHT include myocardial infarction, stroke,

venous thromboembolism, systemic lupus, rheumatoid arthritis, urinary incontinence and asthma. The long-term risks associated with CHT are an increase in breast cancer, increase in gallbladder surgery or gallbladder cancer, an increase in memory and hearing loss, possible increase in dementia and endometrial cancer. Dr. Colditz concludes that

> [L]ong term combined hormone therapy should not be used. Furthermore, short-term hormone therapy should only be used by women with severe and persistent menopausal symptoms after non-hormone based approaches have been tried.

147. I have also reviewed report of David Buckley and Donald Austin regarding the results of their review and analysis of data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (data from 1974-2001). I note that they found a statistically significant increase in "the proportions of ILC (invasive lobular carcinoma) and Mixed Ductal/Lobular cancer relative to all invasive breast carcinoma." The increased proportion was observed only in women in the postmenopausal age group. Further, and most importantly, the "disproportionate increase in ILC and mixed lobular/Ductal carcinoma trend was detectable as early as 1981" and remained "significantly elevated and increasing each year for the next 20 years." Austin and Buckley conclude, "[t]his finding is consistent with a new or expanding exposure in the susceptible population, i.e., women age 50 and over."

148. In 1990, Glass and Hoover reported the results of their review of data from the Kaiser Permanente cancer registry.[17] The population sample included all newly diagnosed breast cancers among members of the Kaiser Permanente health plan between 1960 to 1985. The study reported a 45% overall increase in the incidence of breast

[17] Glass A.G., Hoover R.N., Rising incidence of breast cancer: relationship to stage and receptor status, J Nat Can Inst.; 1990, April 18; 82(8)

cancer with the greatest increases seen the women 60 years of age or older (74% increase) and those between 45 and 59 years old (36% increase). Even more substantial, however, was the finding of an increase in estrogen receptor positive breast cancers between **1974-1985** of an average 131%.

149. Upjohn, as a pharmaceutical company manufacturing, marketing, and profiting from combination hormone therapy with a responsibility to market a safe and effective product to the public should have monitored cancer registries and the medical literature for signals of increasing breast cancer in menopausal women receiving exogenous hormones. Upjohn should have monitored the medical literature and case reports because early animal studies suggested the potential increased risk of breast cancer. This is particularly true after it began to aggressively promote an unapproved use of Provera to physicians with recommendations for prolonged prescription with exogenous estrogen. Upon detecting a signal such as the Glass and Austin/Buckley describe, a reasonable pharmaceutical company would have endeavored to ascertain, through well-designed clinical studies, patient monitoring, or further animal studies the degree of association between combination hormone therapy and breast cancer. A responsible pharmaceutical firm would have also taken steps to comply with the Act and to update its package insert.

150. From 1975 through 2002 the Provera package insert published in the PDR, and the present product label (revised April 2004) made no reference to the increased risk of breast cancer in humans associated with use of the drug in CHT. No past or current label warns of whether the addition of a progestin to estrogen in hormone therapy increases, or may increase, the risk of breast cancer in women. Further, no Provera product label

identifies the other long and short-term risks of combination hormone therapy as specified in Dr. Colditz' report. This is surprising given Upjohn's 1986 letter to the FDA (NDA-PRO 0011628) in which it argues that "it is inappropriate to communicate important prescribing information concerning drug safety in one package insert (i.e. the estrogen insert) yet fail to incorporate the same information" in Provera's package insert. Upjohn's position in this letter reflects an acknowledgement of its responsibility to the medical community, and to patients, to communicate adequate information about the safety of combination hormone therapy.[18] Upjohn failed in this regard.

151. Since at least 1975 through today, the second paragraph under the Warnings heading in the Provera package insert has stated

> Beagle dogs treated with medroxyprogesterone acetate developed mammary nodules, some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature, whereas the nodules in the drug-treated animals were larger, more numerous, persistent, and there were some breast malignancies with metastases. Their significance with respect to humans has not been established.

152. Donald Demke, Pfizer's corporate designee for Upjohn's drug safety procedures testified by deposition on January 19, 2005. When asked whether an association between medroxyprogesterone acetate with or without conjugated estrogen and breast cancer he responded:

> I reviewed the package information, and the—there was – well, breast cancer was not labeled. There was not an association. There was some discussion of dog studies, but that does not make it labeled when you're talking about animals. So, breast cancer is not a labeled event for Provera.

[18] Furthermore, David Engels assertion that physicians were warned of a risk of breast cancer in combination hormone therapy by reference to the estrogen label (David Engels Deposition, pages 194-5) is undermined by Upjohn's 1986 statement.

(Demke Deposition p. 360, lines 11-24).

As such, the warning pertaining to beagle dogs was not, and is not a statement relating to an association between Provera and breast cancer in humans. Upjohn, as a pharmaceutical company that was financially benefiting from the use of Provera had a duty to conduct follow-up animal studies to ascertain the significance of the tumors seen in beagle dogs.

153. Despite the findings of the WHI study, Provera's label has not yet been amended to reflect the new safety/risk data. According to Pfizer's corporate designee David Engels, "...the labeling changes that we've suggested are at the FDA. So, it's up to the FDA right now."

VI. Standards of Care

154. The FDCA provides a minimal standard for a drug product to be able to enter the marketplace. The FDCA prohibits any manufacturer of any FDA-regulated product, food, cosmetic, biologic, drug and device to sell a product in the United States which is in violation of the Act (21 USC Sec. 301[331]). For drugs, biologics, and devices, the manufacturer under current Good Manufacturing Practices (GMP) is required to ensure that it sells safe and effective products to the public both before and after product approval and that, a product is adequately and truthfully labeled, with adequate warnings and truthfully promoted. All United States pharmaceutical companies are required to have in place written standard operating procedures (SOP) in order to continuously monitor the performance of their facilities, the quality of products produced at facilities and the reported performance of its product in order to remain in full compliance with the Act.

155. Regarding the new drug approval process, the FDA has always been dependent on the drug manufacturer, the sponsor, to provide it with complete, accurate, timely and truthful information about the risks and benefits of a proposed new drug produc, in its amendments, reports and supplement filings with FDA. FDA is required to use the information provided to it by the sponsor in a marketing application and related documentation to make initial determinations regarding risk versus benefit and whether to allow the start of marketing of a new drug in the United States. The FDA's decision and actions regarding new drug approval or denial of an NDA directly depends on the diligence of the manufacturer for complying with the Act, having appropriately tested its new drug during both during preclinical and clinical stages, and then disclosing to FDA, in a truthful, timely and accurate manner all material facts, all information concerning the safety and utility of its drug, all product performance, risks and benefits to the public, and scientific support for safety and efficacy in treatment of a condition or disease. The manufacturer's obligations under the Act, to both FDA and the public, are continuing in nature, and encompass both the pre-approval and post-approval stages of the drug's product life.

156. The responsibility for the adequacy of testing and development of a new drug, design of product insert, advertising and promotions to physicians has rested with the NDA sponsor and not with the FDA. The FDA issues nonbinding Guidances for industry to help it utilize methods for a sponsor to support safety and efficacy for a new indication as required by the Act in terms of NDA marketing applications and the "least burdensome methods." These FDA Guidances are nonbinding. FDA suggests and

comments but the ultimate responsibility for compliance with the Act and support of safety and efficacy, adequacy of labeling and product performance rests with the firm.

157. The FDA is not intended as an agency to engage in the development of new drugs. The FDA does not design the clinical and pre-clinical studies for a sponsor to support gaining marketing approval by an NDA. FDA does not tell a drug sponsor when it should file an IND, NDA or sNDA (Supplemental New Drug Application) (See discussion below). It is the drug's sponsor or its United States agent that is responsible for performing these functions to attempt to market a new drug and comply with the Act.

158. After the Kefauver-Harris Amendment to the Act, an original NDA must be supported through the use of well-designed human clinical investigations (Investigational New Drug Application (IND))(21 CFR part 312) published by FDA in March 1987, 52 FR 8831. A new drug application (NDA) was to contain all of the required elements described by the Agency 21 USC Sec 505 [355], and 21 CFR part 314. In addition, the FDA was empowered by Congress with a greater pharmacovigilance role after new drug approval to help ensure continued safety and efficacy of a new drug and protection of the public when a drug was used for treatment of commercial patient populations.(21 USC Sec 505(k) [355], 21 CFR 314.80 published 1985, 50FR21238). The FDA was required to monitor product inserts, labeling and promotion of approved new drug applications to help ensure the sponsor's compliance with the Act and the safety of the public. (21 USC Sec 301[331], Sec. 501[351], Sec. 502[352] and 21 CFR 201,202, and 203).

159. Finally, it is the ultimate responsibility of a United States pharmaceutical company to ensure that the products it manufactures, markets in the United States, and

profits from are reasonably safe and effective for the intended population and indication, are adequately labeled, and are truthfully marketed.

VII. Summary of Opinions

160. Based on my experience, education and training, and review of the documents and the expert reports of Colditz and Austin/Buckley, it is my opinion, which is made to a reasonable degree of professional certainty, that Pfizer, Pharmacia & Upjohn, and The Upjohn Company (collectively referred to as "Pfizer") failed to act as a responsible pharmaceutical manufacturer when it: 1) failed to adequately warn doctors and patients, whom Pfizer clearly recognized were prescribing/ingesting Provera with estrogen in combination hormone therapy, that the potential risks outweighed the potential benefits (potential risks included the risk of invasive breast cancer and cardiovascular effects), and further failed to warn physicians and patients that Pfizer had never assessed those increased risks through animal or clinical studies or pharmacovigilence; 2) failed to warn physician and patients of CHT's association in the medical literature with production of increased breast density – itself an increased risk factor for breast cancer[19]; 3) consistently ignored its responsibilities as a United States manufacturer to comply with the requirements of the Food, Drug and Cosmetic Act; 4) aggressively promoted Provera to physicians and patients as suitable for use in combination hormone therapy without first having obtained scientific support for the safety and effectiveness of that indication; 5) marketed Provera to physicians and their patients post DESI without adequately informing physicians of the lack of efficacy findings of the NSA-NRC and FDA in the DESI process for treatment of menopause symptoms and as a combination hormonal therapy with estrogen; 6) persisted in its pre-DESI misleading promotions and marketing

[19] Report of Jasenka Demirovic, MD, MSC, PhD

practices implying that PROVERA was safe and "effective" for combination hormone therapy (CHT) in postmenopausal women, and effective for opposing the effects of estrogen and able to reduce the "hidden risks" of endometrial cancer from unopposed estrogen.

161. It is clear from the records that Pfizer marketed Provera to physicians as if it were a pre-1962 drug (*pre-DESI drug) and a "Pre- Kefauver-Harris Amendment" FDA. Post-DESI, Pfizer failed to update its operating procedures to acknowledge that it must first obtain valid scientific evidence through well-conducted, randomized clinical trials as required by the Act. Simply put, Pfizer failed to act as a reasonably prudent pharmaceutical company when it refused to adapt to a changing regulatory environment, disregarded the role of the FDA to protect public health, disregarded the role of the physician to do no harm, and disregarded its duty to comply with the Act.

162. Pfizer failed to act as a reasonably prudent pharmaceutical company when it failed to conduct adequate valid clinical studies regarding the health consequences of prolonged combination hormone therapy in menopausal women and failed to put together and conduct its own well- designed prospective studies capable of supporting approval of Supplemental NDAs for its new indications. Pfizer took no actions to monitor patient outcomes and safety or to review reports in the medical literature to determine whether PROVERA was indeed safe and effective for the indication in light of :1) Pfizer's decision to promote Provera to physicians for use with unopposed estrogen as a combination hormone therapy in postmenopausal women; 2) Pfizer's knowledge that Wyeth, the world's leading menopausal estrogen manufacturer, was promoting combination hormone therapy with MPA to provide long-term "uterine protection" to

women taking unopposed estrogen; 3) Pfizer's knowledge that its promotion to physicians for an unapproved use in postmenopausal women had been effective in light of soaring sales attributed to the prescription of Provera in CHT.[20] In short, Pfizer chose to do nothing to investigate whether there were new unacceptable risks introduced by its recommending to physicians that they increase patient exposures to PROVERA in combination with long-term estrogen in hormone therapy.

163. Despite signals in the medical literature, cancer registries, and the IARC's designation of estrogen as a human carcinogen and medroxyprogesterone acetate (MPA) as "possibly carcinogenic" in humans, Pfizer remained silent to physicians and women. Pfizer failed to adequately warn physicians and patients in product labeling, advertsing or or promotions at any time of an increased risk with increasing Provera exposure, or a potential increased risk from exposure, for breast cancer in postmenopausal women receiving prolonged combination estrogen/progestin hormone therapy.

164. Pfizer failed to act as a reasonably prudent United States pharmaceutical company when it repeatedly ignored the efficacy findings of the DESI Review panel and the safety concerns behind the FDA's request for patient labeling warnings for estrogen and progesterone. Pfizer ignored FDA's multiple requests that it NOT promote its product to physicians and patients for unapproved indications, a violation of the Act. It is my professional opinion that Pfizer's conduct demonstrated a lack of concern for the safety of postmenopausal women, deviated from the obligations of a reasonably prudent United States pharmaceutical manufacturer by misleading physicians and women about the risks

[20] RM_AA-01561147-8; Roehl Deposition Exhibit 16; ' "...70% of progestins are prescribed for use together with estrogens" Affidavit of Jeffrey S. Simpson, Upjohn v. Wyeth, April 18, 1995.

of prolonged Provera exposure. Such actions have proximately resulted in exposing postmenopausal women to the risks of prolonged combination hormone therapy (CHT).

I reserve the right to amend my opinions.

Suzanne Parisian, MD

SUZANNE PARISIAN, M.D

CURRICULUM VITAE

EMPLOYMENT HISTORY:

8/95- **PRESIDENT**
MEDICAL DEVICE ASSISTANCE, Inc.
7117 N. 3rd Street
Phoenix, Arizona 85020

12/1993-7/95 CHIEF MEDICAL OFFICER
Division of Reproductive, Abdominal, Ear, Nose and
Throat, and Radiology (DRAERD)
OFFICE OF DEVICE EVALUATION (ODE)
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)
FOOD AND DRUG ADMINISTRATION (FDA)

8/1991-7/95 Commander
United States Public Health Service

8/1991-3/1993 Medical Officer
Office of Health Affairs (OHA)
Center for Devices and Radiological Health(CDRH)
FOOD AND DRUG ADMINISTRATION (FDA)

4/1993-11/93 Medical Officer
Division of Reproductive, Abdominal, Ear, Nose &
Throat, and Radiology (DRAERD)
Office of Device Evaluation (ODE)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration (FDA)

8/1991-7/95 Clinical Staff Appointment
Office of the Medical Examiners for Armed Forces
Armed Forces Institute of Pathology (AFIP)
Washington, D.C.

4/1985-6/1987 General Practice
Avtex Fibers, INC
Front Royal, Virginia

4/1980-7/1981 Emergency Medicine
President
Mountain Emergency Medical
Caldwell Memorial Hospital
Lenoir, North Carolina

10/1979-3/1980 General Practice
Caldwell County Health Department
Lenoir, North Carolina

CDRH / FDA /HHS & USPHS HONORS:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Employee of the Month August 1993

FOOD AND DRUG ADMINISTRATION
Employee of the Month August 1993

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
Employee of the Month August 1993

Public Health Service's Achievement Medal- 1992

Public Health Service's Unit Commendation Medals
Acupuncture Workshop- 1995
Total Parenteral Nutrition Complications Group- 1995
Night Vision Equipment Radiation Leak Group- 1995
Anesthesia Heated Wire Circuit-1994
Small-Bore Anesthesia Group-1992
Corporate-Wide Injunctions Groups-1993, 1994, 1995

Public Health Service's Commendation Medal
Neonatal Ventilators-1992
Hemodialyzer Reuse Labeling-1995

Public Health Service's Unit Citations- 1992, 1992
Latex Allergy-1993

Nominee for FDA Honor Award
FDA's Policy for Hyperthermia Clinical Trials-1995

Certificate of Appreciation CDRH's Staff College
Clinical Trials Course, Spring, 1995

Other Honors

University of Central Florida, *Cum Laude*, 1974

University of Central Florida, *Summa Cum Laude*, 1975

REGULATORY ACTIVITIES:

OFFICE OF DEVICE EVALUATION (ODE) PRIMARY RESPONSIBILITY:
Primary responsibilities included:

1) **Review of FDA Premarket applications-** 510Ks,Investigational Device Exemption(IDEs), Premarket Approval Applications (PMAs)) including design, labeling, health issues and quality systems requirements for manufacturing issues; INDs.
2) **Review and evaluation of clinical trials, etc;**
3) **Design of Post Marketing Clinical Studies;**
4) **Health Risk Assessments and management for Office of Compliance and the FDA District Field Offices;**
5) **Liaison for manufacturers, clinical investigators, government agencies, medical community, press, Congress, patient advocate groups, public, and manufacturer's organizations;**
6) **Training of ODE clinical reviewers;**
7) **Quality Assurance design;**
8) **Identification and resolution of safety and efficacy issues;**
9) **Presentation of clinical device issues to FDA Advisory Panels;**
10) **Presentation of Device-related issues to Health Care Financing Administration's Technology Assessment Committee (HCFA, TAC);**
11) **Investigator and Manufacturer Guidances from CDRH for Clinical Protocols;**
12) **Clinical support for FDA regulatory actions and hearings.**

CLINICAL DEVICE RESPONSIBILITY AREAS in ODE:

ENT - Cochlear implants, brainstem implants;
Radiology - Magnetic Resonance Imaging, Ultrasonography, Mammography, Radiation Hyperthermia Therapy, Neurosurgical Imaging Systems, Interventional Radiology, Thermography, Radiotherapy;
Urology- cryosurgery, lasers, stents, penile prostheses, urethral implants, lithotripsy;
Extracorporeal circulation - Hemodialysis, LDL-Apheresis, Plasmapheresis, Immunadsorption, Cell Harvest;Organ Preservation;
Pulmonary- bronchoscopy, stents;
Gynecology- infertility, PAP smear technology;
Obstetrics- chorionic villus sampling, amniocentesis, fetal monitoring;
Gastroenterology- biliary stents, neuromuscular stimulators;
Endoscopy & Laparoscopy; Lasers;
Alternative Medicine; Immunology;
In vitro diagnostics; Toxicology; Cytology;
Biological Artificial Organ Assist Devices (Center for Biologics Evaluation and Review (CBER);
Implanted Neuroelectrical Stimulators;
Genetics; Perinatology;
Transfusion Medicine; Electromagnetic Fields and Interference;
Tissue and Organ Transplantation (CBER);
Forensics
Combination Products
Contrast Agents

100 Health Risk Assessments while in ODE

OFFICE OF HEALTH AFFAIRS PRIMARY RESPONSIBILITY :

1) Primary support for Office of Compliance-
Health Risk Assessments & Health Hazard Evaluations; review of Labeling, Mandatory Device Reports (MDRs), Adverse Experience Reports (AERs)
2) Interaction with manufacturers, investigators, health care providers, professional organizations;
3) Interaction with FDA District Offices, other government agencies, the Office of Device Evaluation;
4) Identification of public health and safety issues.

Primary Clinical Responsibility Areas for OHA:
Cardiovascular; Anesthesia; Pulmonary Medicine; Orthopedic Surgery; Unconventional Therapies; Rehabilitative Medicine; Pathology; Home Health;

Emergency Medicine; Hemodialysis

162 Health Risk Assessments while in OHA

FORENSIC MEDICINE CLINICAL ACTIVITIES:

Evaluation of Patient Death with Retained Radioactive Source

Medical Review of patient deaths and possible role of breast implants.

Dover Port Mortuary Medical Examination of Military
Personnel-Persian Gulf Area Deaths
Dover, Delaware

Review and Final Sign-Out of Military, Dependent,
FBI and CIA Autopsy Cases
Armed Forces Institute of Pathology
Office of Medical Examiner
Washington, D.C.

Center for Devices and Radiological Health (CDRH) Assigned Support:

Anesthesia Post Market Surveillance Chairman (1992- May, 1993)
FDA and CDRH's Liaison for Alternative Medicine
CDRH Staff College Instructor, Clinical Trials
Temple Tier II Report-ODE's Internal Quality Assurance Review of Selected Medical Device Premarket Evaluations

CDRH's Representative
National Kidney and Urological Diseases Advisory Board
National Institutes of Health
Health Care Financing Administration's Technology Assessment Committee
Ad Hoc Working Group CDRH Transfusion Medicine

CDRH's Support for FDA's Office of Legislative Affairs and Press Office for:
Extracorporeal Hyperthermia and treatment of patients with AIDS;
Alternative Medicine;
Hemodialysis;
Acupuncture Needle Reclassification.

LECTURES While at FDA:

Armed Forces Institute of Pathology
Essentials of Medical Devices and Death Investigations
Washington, D.C.
October, 1993

Third World Conference of Acupuncture
FDA's Viewpoint of Acupuncture
Kyoto, Japan
November, l993

Alternative Medicine Conference
FDA's Viewpoint of Acupuncture
Smithsonian Museum of Medicine
National Museum of Medicine
Washington, D.C.
December, 1993

Reuse of Hemodialyzers
Office of Device Evaluation
Presentation of CDRH Draft Guidance Document
Rockville, Maryland
December, 1993

Office of Alternative Medicine/National Institutes of Health (OAM/NIH)
Workshop for Acupuncture Needle Reclassification
FDA's Viewpoint, and Served as Panel Chairman
Rockville, Maryland
April, 1994

National Acupuncture and Oriental Medicine Alliance
Annual Conference
FDA's Viewpoint for Regulation of Acupuncture Needles
Crystal City, Virginia
May, 1994

OAM/NIH and FDA's Workshop Planning Group
for Herbs Conference, CDRH's policy
For Alternative Medicine Providers
Rockville, Maryland
May, 1994

American Association for Medical Instrumentation (AAMI)
CDRH's perspective on the Hemodialysis Reuse Labeling Guidance
Washington, D.C.
June, 1994

AAMI Conference
FDA's Recommendation for Hemodialyzer Reprocessing Labeling
Hemodialysis Reuse Section
Washington, D.C.
June, 1994, November 15, 1994
& May 9, 1995 (Joint AAMI/HIMA Workshop)

FDA's Genitourinary Advisory Panel
Presentation of the Hemodialysis Reuse Labeling Guidance
Rockville, Maryland
July, 1994 &
January 1995

Presentation of 2 LDL-Apheresis PMA applications
Kaneka's Liposorber LA-15 System
B.Braun of America's H.E.L.P. System
Rockville, Maryland
April, 1995

FDA's ENT Advisory Panel
Presentation of Cochlear's Nucleus 22 Cochlear Implant
PMA application for expansion of patient population
Rockville, Maryland
April, 1995

Second Symposium of Society for Acupuncture Research (SAR)
Georgetown University Conference Center
Government's perspectives on clinical trials for acupuncture
Washington, D.C.
September 17, 1994

LECTURES, INTERVIEWS & ACTIVITIES After FDA:

FDA and Acupuncture
ABC News Interview
Los Angeles, CA
Summer 1995

Dealing with Adverse Events
1996 National Sales Meeting
Johnson & Johnson Medical Inc.
Dallas, Texas
April 1, 1996

Dialyzers Labeled for Reuse
The Manufacturer's Responsibilities
Fifth Annual Spring Clinical Nephrology Meeting
National Kidney Foundation
Anaheim, CA
April 27, 1996

Challenges with Infusion Therapy Complications
Intravenous Nursing Society
Charlotte, North Carolina
May 7, 1996

510(k) Tutorial
Food Drug and Law Institute
40th Annual Educational Conference
Washington, D.C.
December 9, 1996

FDA Expert Panel Member
Medical Devices: Device Labeling Requirements
Center for Devices and Radiological Health
Food and Drug Administration
Rockville, MD
September 5, 1997

Science and "Art" of Designing Successful "Medical Device" Clinical Trials for the FDA- A Workshop
Institute for International Research, Pharmaceutical Division
Santa Monica, CA
September 22-24, 1997

What You May Need to Know about Medical Devices
And FDA But Never Would Have Thought to Ask.
22nd Annual Great Lakes Biomedical Conference
Engineering in Medicine and Biology Society
Milwaukee School of Engineering
Milwaukee, Wisconsin
April 3, l998

ABC News Interview with Ron Regan
Medical Device Reporting for Surgical Trocar Injuries
WEWS ABC - Channel 5 News
Cleveland, Ohio
May 17, 2001

Interview in :***The Trouble with Trocars***
By Linda Carroll & Alfred Lubrano
Smart Money
The Wall Street Journal Magazine of Personal Business,Hearst Communications
New York, NY
November 2001

FDA Inside and Out- Public Health Issues in Cervical Cancer Screening
Global Vista Medical Foundation
Sponsored by President Medical technologies Co., LTD
Taipei, Taiwan, R.O.C.
March 3, 2002

Inside the FDA
Presentation to Kent County Medical Society
Grand Rapids, MI
May 14, 2002

Clinical Trials
Medical Grand Rounds
St. Mary's Hospital
Grand Rapids, MI
May 15, 2002

Interview in ***The Risky World of Medical Implants***
A Three Part Series
Robert Cohen and J. Scott Orr
Star Ledger
Morris Edition, New Jersey
August 11-13, 2002

NBC's Dateline Interview with Lea Thompson
Special Investigations- **Do No Harm-Sulzer's Hip Recall**
NBC News Washington
Washington, D.C.
*2004 Emmy Outstanding Investigative Reporting Business News Story
*2004 Edward R. Morrow Television Investigative Reporting
July 25, 2003

Interview with Author Barbara Seaman
History of FDA's Clearance of Bone Densitometers, page 78
The Greatest Experiment Ever Performed on Women
Published by Hyperion, New York, New York
Fall 2003

Interview **Is This Any Way to Have a Baby? The Terrifying Truth About Fertility Drugs.**
Barbara Seaman and Joanna Perlman
OPRAH Magazine, beginning page 188
Published by Hearst Communications Inc., New York, New York
February 2004

Interview **Warning! The Medical "Miracles" That May Be Hazardous to Your Health.**
Alexis Jetter
Good Housekeeping Magazine, beginning page 138
Published by Hearst Communications Inc., New York, New York
March 2004

Impact of the FDA Ban On Litigation
Defense & Plaintiff Views
Mealey's Ephedra Litigation Conference
San Diego, CA
May 11, 2004

Interview **Investigation of FDA's Oversight of Mammography Facilities**
Producer Mary Schwager
Investigative News
WHDHTV-NBC
Boston, MA
October 19, 2004

Bayer Stroke Trial Continues
Tim Gurrister
Top of Utah
Salt Lake City, UT
January 22, 2005

Drugs, Informed Consent and Monitoring to Ensure Safety of Women for Stem Cell Donation
Open Letter of Suzanne Parisian, MD
Presented to California Legislature and Massachusetts Legislature
Released **February 2005**

Open Letter Suzanne Parisian, MD
Chapter 25- **Infertility and Assisted Reproduction**
Emerging Biotechnologies: Cloning
Our Bodies Ourselves
Boston Women's Health Book Collective, Inc.
Boston, MA
March 2005

Interview **Stem Cell Research & Egg Donation**
Martha Bebinger
WBUR NPR Radio
Boston, MA
April 2, 2005

Interview in **Exposed Nerve**
Craig Malisow
Houston Press
Houston, TX
April 7, 2005

Statement-Two Pending PMAs
On Behalf of ProChoice Alliance for Responsible Research (PROCARR)
General & Plastic Surgery Devices Panel
Center for Devices and Radiological Health
Food and Drug Administration
Gaithersburg, MD
April 11, 2005

Review of the FDA's History of Silicone-Gel Filled Breast Implants
Briefing of US House of Representatives and US Senate Staff
Washington, DC
April 25, 2005

Statement – Two Pending PMAs
Presentation to FDA Commissioner Dr. L. Crawford
Food and Drug Administration
Washington, DC
April 26, 2005

Statement – Two Pending License Applications
Health Canada Therapeutic Products Expert Review Panel
Ottawa, Canada
September 29, 2005

FDA & CLIA
Trends in Medical Diagnostic Commercialization
Arizona Biotechnology Association
Phoenix, AZ
February 7, 2006

FDA's CHAIRMAN
Reuse of Hemodialyzer, A Workshop
Rockville, Maryland
December 10, 1993
May 1995

VOLUNTARY STANDARDS COMMITTEE INVOLVEMENT

Has been an active member of the following committees for
AMERICAN SOCIETY for TESTING MATERIALS (ASTM)
Medical and Surgical Material and Devices
Occupational Health and Safety
Search and Rescue
Anesthetic and Respiratory Equipment
Forensics
Biotechnology

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION (AAMI)
Renal Disease and Detoxification Committee

PUBLICATIONS:

Homoeotic Effect of the Tumorous-Head Mutant and Differential Effect of an Enhancer Gene in the Tumorous-Head Strain of Drosophila Melanogaster,
Canadian J Genet. and Cytology, 1975; 17:423-432.

Latex Allergy and Anesthesiology.
Anesthesia Patient Safety Foundation Newsletter
Spring, 1992.

The Potential for Adverse Reactions Due to the Presence of Additives and Preservatives in Intravenous Solutions and Medications; Journal Vascular Access Devices, Winter 1996, Vol 1 (1): 5-14.
*Sponsored by Johnson & Johnson Medical, Inc.

Letter to the Editor, Midline Catherization in Hospitalized Patients.
Annals of Internal Medicine, October 15, 1996; Vol 125, No 8: p 697.
*Sponsored by Johnson & Johnson Medical, Inc.

FDA INSIDE and OUT,
S. Parisian, M.D.
Publication May, 2001
Fast Horse Press, Inc.

DATE AND PLACE OF BIRTH:

September 20,1952,
Rapid City, Pennington County, South Dakota

MARITAL STATUS:
Married- August 26, 1977

FAMILY:
Son 02/09/1985
Daughter 09/12/1986

MEDICAL LICENSURE:
State of Virginia
State of Arizona

EDUCATION:
6/1970-6/1974 Bachelors of Science
University of Central Florida
Orlando, Florida

7/1994-6/1975 Masters of Science
University of Central Florida
Orlando, Florida

7/1975-6/17/1978 Medical Doctorate
University of South Florida
Tampa, Florida

TRAINING:

7/1/1978-6/30/1979 Flexible Internship
Greenville Hospital System
Greenville, South Carolina

9/14/1981-6/30/1982 Pathology Resident
University of California, San Diego
San Diego, California

7/1/1982-2/29/1984 Pathology Resident
University of Southern California
Los Angeles County Medical Center
Los Angeles, California

1/4/1988-1/30/1990 Pathology Resident
Grand Rapids Area Medical Education Center
Grand Rapids, Michigan

BOARD CERTIFICATION:

Board Certified in Anatomic and Clinical Pathology, 1989, American Board of Pathology
College of American Pathologists, Fellow (FCAP)
American Society of Clinical Pathologists, Fellow (FASCP)

SOCIETIES:

Maricopa County Medical Society
American Advancement for Medical Instrumentation
American Society for Testing Materials
Regulatory Professionals Society
American Medical Association
Food and Drug Law Institute
College of American Pathologists
Food and Drug Alumni Association

OFFICE ADDRESS:

MEDICAL DEVICE ASSISTANCE, Inc.
7117 N. 3rd Street
Phoenix, Arizona 85020
Phone: (602) 354-8491
FAX: (602) 354-8696
E-Mail: info@mdassist.com

WEBSITE:
http://www.mdassist.com

2/15/06

SUZANNE PARISIAN, M.D.
4 Year History

COURT TESTIMONY
2002- 2006

01/20-24/05 Marlus Hardy v. Bayer Corporation
Second Judicial District Court
Civil No. 010902836 PL
Weber County, State of UT

03/26/03
Lois and John Barthold v. Target Therapeutics, Inc, Boston Scientific Corporation
State of New York Supreme Court County of Oneida
Index No. 97-2176
Utica, NY

01/23/02
Shows v. St. Dominics Hospital
Hinds County Circuit Court No. 93-75-19
The State Courts of Mississippi
Jackson, MS

DEPOSITION TESTIMONY
2002- January 16, 2006

01/16/06
John and Jane Doe2, Individually and as Guardians ad litem of Minor Child Doe 2
v. Ortho-Clinical Diagnostics, Inc.
United States District Court, Middle District of North Carolina
Case No. 1:03CV00669
Charlotte, NC

01/04/06 Martha Stewart v. Sulzer Ltd., et al.
Superior Court of the State of California Case No: BC 262780
County of Los Angeles, CA

12/16/05
11/10/05

Renee Contratto v Ethicon, Inc(dba Gynecare Worldwide), Johnson & Johnson, Lifecore Biomedical Inc., Vital Pharma, Inc.
Case No. C-03-3804 ARB
United States District Court
Northern District of California
Sacramento, CA

11/09/05

V. Buonocore, Estate of C. Buonocore v. Catholic Healthcare West, Sequoia Hospital, Cardeon Corporation, et al.
CIV 438695
Superior Court of State of California
County of San Mateo, CA

9/08/05

Estate of Estle Dutschke v Hoveround Corporation
Case No. 3:03-CV-00704-MO
US District Court Western District of Kentucky
Louisville, KY

7/15/05

Brian Renovitch v Teton County Hospital District, Synthes, Inc.
Civil No. 04-CV-188-J
For the District of Wyoming
Jackson, WY

7/11/05

Grother, Bender , Williams v M. Meriwether; Doctor's Hospital of Sarasota; Clarus Medical Systems, Inc. and Surgical Innovations and Service Company
Case No. 98-6451-CA-01
Circuit Court of the Twelfth Judicial Circuit in and For Sarasota County, FL
Sarasota, FL

12/01/05
06/10/05

Brenda & Paul Saban v. Idaho Urgent Care, Lumenis Inc., Coherent Inc.
District Court of the Seventh Judicial District State of Idaho

Case No. CV-03-1340
County of Bonneville, ID

05/13/05

Moses Ashford, Sr. for Mary Bell Ashford (deceased) v. Brian Center of Central Columbia, Inc. and Mariner Post-Acute Network
Civil Action No. 00-CP-40-4682
County of Richland, SC

05/24/05
05/03/05 P. Vinion and C. Riddle v. Amgen Inc. and Immunex Inc.
United States District Court for District of Montana
C V 03-202-M-DWM
Missoula Division, Montana

02/02/05

John Doschadis v. Zimmer, Inc.
United States District Court for the District of Minnesota
Case No. 03-CV-6439
Minneapolis, MN

03/15/05
03/14/05
12/06/04
12/07/04

Carlos Johnson, et al. V. Ethicon, Inc., Johnson & Johnson Health Care Systems Consumer Litigation
Charlestown, West Virginia

11/11/04 Roger Allan v. Terens, et al.
Docket No. M 10-L-3030-01
Middlesex County, NJ

10/27/04

Marlus Hardy v. Bayer Corporation
Second Judicial District Court Civil No. 010902836
Weber County, UT

9/21/04 Juliet Cueva v. FKA Sulzer Orthopedics, Ltd., et al.

Superior Court of the State of California Case No: 01CC07945
County of Orange, CA

9/10/04

Mary K Paulin v. Aventis Pasteur Inc., et al.
Bibb County Circuit Court Case N. CV-2002-190
Birmingham, AL

8/24/04

Kirsten Ross v. Cyberonics, Inc.
Case No. SCV 14716
Superior Court of State of California
In and For the County of Placer
Sacramento, CA

5/26/04

Robert G. Oakberg, Ph.D. v. Zimmer, Inc.
United States District Court for District Court of Montana
Cause No. CV-03-47-BU-SHE
Butte Division, MT

5/26/04

Allen Lillebo, Evelyn Reiling, v. Zimmer, Inc.
United States District Court for District Court of Minnesota
Case No. 03-2919, Case No. 03-2920.
Minneapolis, MN

2/25/04

F. George v.. Aultman Hospital, Cardiovascular Consultants, Inc., et al.
New Philadelphia, OH

9/12/03 Dr. D. Teperson v. Centerpulse Orthopedics Inc., FKA Sulzer Orthopedics Inc.
11th District Court of Harris County
Houston, TX

8/19/03

Bartlett, et al. v. Stryker Corporation, et al.
United States District Court for Eastern District of Virginia
Civil Action No. 03-524-A
Alexandria District, VA

5/01/03

R. Morton, M. Morton v. George Washington University, et al.

Superior Court for District of Columbia
Civil Action No.:99CA 004599
Washington, DC

7/08/03
4/03/03

Fred Galzerano v. Stryker Corporation, et al.
Circuit Court of Fairfax County
Law no. 195090
Fairfax, VA

10/10/02

Mindy Cohen and David Cohen v. Dr. F. DiSpaltro, Lysonics, Inc, Misonix, Inc,
Superior Court of New Jersey Law Division-Essex County
Docket N. ESX-L-3040-99
Newark, NJ

9/19/02

Billye K Drinkwater and Henry Drinkwater v. Boston Scientific Corporation
14th Judicial District
No. 01-1509-A District Court of Dallas County
Dallas, TX

7/16/02

Crawford Duane Parker, III v. Alcon Laboratories, Inc.
Cause No. 17-183717-00
District Court
Tarrant County, TX

5/6/02

Dennis Fowler, as Personal Representative of the Estate of Julian Fowler v.
Greater Columbia, Area Healthcare Systems, L.P., d/b/a Providence Hospital and
General Electric Company and ADAC Laboratories, Inc.
Case No. 00-CP-40-2138
Court of Common Pleas
County of Richland, SC

1/15/02

F. Chow, MD v. United States Surgical Corporation
Civil Action No. 00-M1228
U.S. District Court, CO

EXHIBIT 8

IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF ARKANSAS
WESTERN DIVISION

In re:	:	**MDL Docket No. 4:03CV01507-WRW**
	:	**4:04CV02271-WRW**
PREMPRO PRODUCTS LIABILITY LITIGATION	:	
	:	
DIANE LAFERRARA	:	**PLAINTIFF**
v.	:	
WYETH, INC., et. al.	:	**DEFENDANTS**

ORDER

Pending is Defendants' Motion to Exclude Drs. Parisian, Blume, and Austin regarding Failure to Test (Doc. No. 27). Responses, replies, and supplements have been filed. Oral arguments were heard on June 24, 2010. After careful review of the pleadings and supporting arguments, the Court finds that Defendants' motion should be GRANTED.

I. STANDARD

A. Burden of Proof

The admission of expert testimony is governed by Rule 702 of the Federal Rules of Evidence, which reads:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.[1]

[1] Fed. R. Evid. 702.

When a party proffers an expert witness, deciding whether Rule 702 is satisfied is a preliminary issue governed by Federal Rule of Evidence 104(a).[2] Rule 104(a) requires the proponent of evidence to establish its admissibility by a preponderance of the evidence.[3] In determining admissibility, the court is not bound by any of the rules of evidence, except with regard to privilege.[4]

B. Legal Standard for Admissibility

The central inquiry under Rule 702 is whether the proffered expert's testimony is sufficiently reliable.[5] The trial court serves a gate-keeping function, ensuring that any expert testimony is reliable and relevant.[6] It is essential "that the courts administer the Federal Rules of Evidence in order to achieve the 'end[s] that the Rules themselves set forth, not only so that proceedings may be 'justly determined,' but also so 'that the truth may be ascertained.'"[7]

To be admissible, expert testimony must satisfy the two prongs of Rule 702.[8] First, it must be based on scientific, technical, or other specialized knowledge.[9] If the testimony is scientific, it must be grounded in the methods and procedures of science.[10] Likewise, "knowledge" involves more than a subjective belief or an unsupported speculation, requiring instead an appropriate level

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[2]*U.S. v. Martinez*, 3 F.3d 1191, 1196 n.10 (8th Cir. 1993).

[3]*Bourjaily v. U.S.*, 483 U.S. 171 (1987).

[4]Fed. R. Evid. 104(a).

[5]*First Nat'l Bank v. Benham*, 423 F.3d 855, 861 (8th Cir. 2005).

[6]*Id.*

[7]*General Electric Company v. Joiner*, 522 U.S. 136, 149 (1997) (Breyer, J., concurring) (citing Fed. R. Evid. 102).

[8]*U.S. v. Cawthorn*, 429 F.3d 793, 799 (8th Cir. 2005).

[9]*Id.*

[10]*Id.*

of validation.[11] Second, the testimony must be relevant, in that it must help the trier of fact either understand the evidence or determine a fact at issue.[12] The burden of establishing relevancy and reliability rests on the proponent of the expert testimony.[13]

Courts have used a variety of factors to determine the reliability of proffered expert testimony. The most frequently discussed factors are those derived from the Supreme Court's opinion in *Daubert*, where the Court established that the trial court may consider:

> (1) whether the theory or technique can be or has been tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether the theory or technique has a known or potential error rate and standards controlling the technique's operation; and (4) whether the theory or technique is generally accepted in the scientific community.[14]

Because the inquiry is "flexible and fact-specific, a court should use, adapt, or reject *Daubert* factors" as needed, based on the facts of a particular case.[15]

The most recent amendments to Rule 702 added three general standards for courts to use in determining the reliability and relevance of proffered expert testimony. First, the proffered testimony must be based on sufficient facts or data.[16] Second, it must be the product of reliable principles and methods.[17] Third, the expert must have applied those principles and methods reliably to the facts of the case.[18]

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[11] *Id.* at 799-800 (quoting *Daubert v. Merrell Dow Pharms.*, 509 U.S. 579, 590 (1993)).

[12] *Id.* at 799.

[13] *Moore v. Ashland Chem., Inc.*, 151 F.3d 269, 278-78 (5th Cir. 1998).

[14] *Benham*, 423 F.3d at 861 (citing *Daubert*, 509 U.S. at 593-94).

[15] *Unrein v. Timesavers, Inc.*, 394 F.3d 1008, 1011 (8th Cir. 2005).

[16] Fed. R. Evid. 702(1).

[17] Fed. R. Evid. 702(2).

[18] Fed. R. Evid. 702(3).

The focus is not on the expert's conclusion, but on the methodology.[19] The proponent of the testimony "need not prove . . . that the expert's testimony is correct, but . . . must prove by a preponderance of the evidence that the testimony is reliable."[20] Determining the validity of an expert's conclusions is the duty of the finder of fact.

II. DISCUSSION

A. Standard of Care and Failure to Test

Plaintiff has failed to meet her burden of showing that Drs. Parisian, Blume, and Austin may be designated as expert witnesses. The witnesses' proposed expert testimony is not expert in nature because Plaintiff is unable to point to the existence of a reasonable standard of care or a custom and practice established by either industry or governmental standards regarding Defendants' duty to test.

At the outset, the Court recognizes that this motion sets forth a very narrow issue: whether Drs. Parisian, Blume, and Austin can be designated as experts to testify about the reasonable standard of care that Defendants should have followed in the continued testing of HRT after it was placed on the market. There is no question that Drs. Parisian, Blume, and Austin have sufficient expertise in their respective fields; however, their expertise does not qualify them to provide a jury with a reasonable standard of care or a custom and practice, for no other reason than one has not been shown to exist. In other words, their testimony could only be a subjective opinion on what they believe Defendants **could have done** rather than what industry or governmental standards **require** them to do.[21]

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[19] *Moore*, 151 F.3d at 275-76.

[20] *Id* at 276.

[21] See *Zenith Elecs. Corp. v. WH-T Broad. Corp.*, 395 F.3d 416, 419 (7th Cir. 2005) (stating that an expert "who invokes my expertise rather than analytic strategies widely used by specialists is not an expert as Rule 702 defines that term").

For example, before FDA approval of a drug, a manufacturer must establish that there has been "adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."[22] Defendants' drug was approved by the FDA in 1994. Plaintiff now offers Dr. Parisian to testify that Defendants violated the standard of reasonable care after the FDA approved their drug. Yet, Dr. Parisian concedes that once a drug is approved by the FDA, the FDA does little to police the drug once it is out on the market.[23]

The same would be true for Dr. Blume possibly testifying that the PhRMA Code is an established standard of care relied on by manufacturers in the field and should be admissible. First, Judge Wilson has already excluded the use of the PhRMA Code as it would likely cause confusion, undue prejudice, and delay.[24] Second, Plaintiff has failed to show how it would be admissible as a standard of care under Arkansas law. Without some established industry standard, Dr. Blume would only be able to subjectively testify about what companies **could** do by the way of testing rather than what Defendants were required to do.

At the *Daubert* hearing on June 24, 2010, Plaintiff's counsel had the opportunity to provide a defined standard of reasonable care in industry custom and practice once a drug has been approved by the FDA and placed on the market. Counsel could not do so. Plaintiff's counsel conceded that

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[22] 21 C.F.R. § 314.125(b)(2).

[23] Dr. Parisian testifed in the *Scroggin* trial that:
The FDA is the government body. Their main function is approval, and there is some postmarketing. But the life cycle of the drug actually belongs primarily to the manufacturer. They are the ones that are required to have written procedures in place to do what they call pharmacovigilance, where they are supposed to watch their product. The FDA gets called into issues when there is a major issue that gets identified. But they don't have the time or resources to monitor everyone's drugs." 4:04-cv-01169-WRW, Feb 12, 2007, Trial Tr. at 1235-1236.

[24] *Rush v. Wyeth*, 4:05-cv-00497-WRW, Doc. No. 473 (01/16/07).

there is not a defined standard for what must occur in each circumstance. In fact, he stated, "depending on the circumstance, a drug company might react differently." Plaintiff's counsel admitted the standard could be different in every circumstance – and therein lies the rub – there is no set standard. Drs. Parisian, Blume, and Austin cannot be qualified as experts simply to testify what they believe Defendants could have done versus what they should have done.[25]

In sum, the testimony Plaintiff seeks to elicit from these doctors is too subjective and not expert in nature. "[T]he word knowledge connotes more than a subjective belief or unsupported speculation."[26] "Proposed testimony must be supported by appropriate validation – *i.e.*, good grounds, based on what is known."[27] Because Plaintiff cannot show some independent objective validation, Drs. Parisian, Blume, and Austin should not be permitted to testify as experts; they simply would be providing their own subjective beliefs about what could have been done.

B. Available Tests

Plaintiff claims that even if her witnesses are precluded from testifying that Defendants violated the reasonable standard of care and were negligent in their failure to continue testing their drug, they still should be able to testify about the types of studies available, their costs, and their

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[25] See *Joiner*, 522 U.S. at 146 (finding that "[b]ut nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered"). The term "ipse dixit" is a legal term meaning "something asserted but not proved." It is literally translated "he himself said it." Black's Law Dictionary 905 (9th ed. 2009).

[26] *Daubert*, 509 U.S. at 590.

[27] *Id.* at 591.

trustworthiness.[28] Defendants counter that "such testimony would be a backdoor attempt to suggest that Wyeth should have conducted those studies."[29]

At present time, the Court is unwilling to preclude all testimony from these witnesses as Defendants request. Depending on a number of factors unknown at this time, this testimony could become relevant and admissible at trial. The Rules of Evidence will govern the admissibility at trial. Nevertheless, Defendants' point is well taken and Drs. Parisian, Blume, and Austin may not testify as to what tests would have been "appropriate" for Defendants to conduct.

III. CONCLUSION

Based on the findings of fact and conclusions of law above, Defendants' Motion to Exclude the Testimony of Drs. Parisian, Blume, and Austin regarding Failure to Test (Doc. No. 27) is GRANTED.

Pursuant to 28 U.S.C. § 636(b)(1)(A) and Local Rule 72.1, the parties have a right of appeal to District Judge Wilson through filing a motion which is due by 5:00 p.m. on July 6, 2010. The specific requirements for appeal are set out in 28 U.S.C. § 636(b)(1)(A) and Local Rule 72.1. The appeal should relate directly to the findings of the Court in this Order and be limited to five (5) pages.

IT IS SO ORDERED this 29th day of June, 2010.

JOE J. VOLPE
UNITED STATES MAGISTRATE JUDGE

[28]Doc. No. 48, p. 2

[29]Doc. No. 57, p. 3

EXHIBIT 9

IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF ARKANSAS
JONESBORO DIVISION

In re:	:	**MDL Docket No. 4:03CV01507-WRW**
	:	**3:05CV00078-WRW**
PREMPRO PRODUCTS LIABILITY LITIGATION	:	
	:	
MARGARET WILSON, ET AL.	:	**PLAINTIFFS**
	:	
v.	:	
	:	
WYETH, INC., et. al.	:	**DEFENDANTS**

ORDER

Pending is Defendants' Motion to Exclude Drs. Parisian, Blume, and Austin regarding Failure to Test (Doc. No. 38). Responses, replies, and supplements have been filed. Oral arguments were heard on June 24, 2010. After careful review of the pleadings and supporting arguments, the Court finds that Defendants' motion should be GRANTED.

I. STANDARD

A. Burden of Proof

The admission of expert testimony is governed by Rule 702 of the Federal Rules of Evidence, which reads:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.[1]

When a party proffers an expert witness, deciding whether Rule 702 is satisfied is a preliminary issue governed by Federal Rule of Evidence 104(a).[2] Rule 104(a) requires the proponent of evidence

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[1] Fed. R. Evid. 702.

[2] *U.S. v. Martinez*, 3 F.3d 1191, 1196 n.10 (8th Cir. 1993).

to establish its admissibility by a preponderance of the evidence.[3] In determining admissibility, the court is not bound by any of the rules of evidence, except with regard to privilege.[4]

B. Legal Standard for Admissibility

The central inquiry under Rule 702 is whether the proffered expert's testimony is sufficiently reliable.[5] The trial court serves a gate-keeping function, ensuring that any expert testimony is reliable and relevant.[6] It is essential "that the courts administer the Federal Rules of Evidence in order to achieve the 'end[s] that the Rules themselves set forth, not only so that proceedings may be 'justly determined,' but also so 'that the truth may be ascertained.'"[7]

To be admissible, expert testimony must satisfy the two prongs of Rule 702.[8] First, it must be based on scientific, technical, or other specialized knowledge.[9] If the testimony is scientific, it must be grounded in the methods and procedures of science.[10] Likewise, "knowledge" involves more than a subjective belief or an unsupported speculation, requiring instead an appropriate level of validation.[11] Second, the testimony must be relevant, in that it must help the trier of fact either

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[3]*Bourjaily v. U.S.*, 483 U.S. 171 (1987).

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[24] *Rush v. Wyeth*, 4:05-cv-00497-WRW, Doc. No. 473 (01/16/07).

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III. CONCLUSION

Based on the findings of fact and conclusions of law above, Defendants' Motion to Exclude the Testimony of Drs. Parisian, Blume, and Austin regarding Failure to Test (Doc. No. 38) is GRANTED.

Pursuant to 28 U.S.C. § 636(b)(1)(A) and Local Rule 72.1, the parties have a right of appeal to District Judge Wilson through filing a motion which is due by 5:00 p.m. on September 22, 2010. The specific requirements for appeal are set out in 28 U.S.C. § 636(b)(1)(A) and Local Rule 72.1. The appeal should relate directly to the findings of the Court in this Order and be limited to five (5) pages.

IT IS SO ORDERED this 16th day of September, 2010.

JOE J. VOLPE
UNITED STATES MAGISTRATE JUDGE

[28] *Laferrara v. Wyeth*, Case No. 4:04-cv-02271 WRW, Doc. No. 48, p. 2.

[29] *Id* at Doc. No. 57, p. 3.